IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE NORTHERN DISTRICT OF CALIFORNIA

CHIRON CORPORATION,
Plaintiff,
vs. CIVIL ACTION NO.
F. HOFFMANN-LA ROCHE LTD, 98-0315 (CV)
HOFFMANN-LA ROCHE INC.,
ROCHE MOLECULAR SYSTEMS, INC.,
ROCHE DIAGNOSTIC SYSTEMS, INC.
and DANIEL W. BRADLEY,
Defendants.
_____/

CONFIDENTIAL

DEPOSITION OF GEORGE KUO, Ph.D.
Monday, November 8, 1999
VOLUME I
Pages 1 to 244

REPORTED BY: FRANCES ANN WEINROB, C.S.R. 4029
CERTIFIED REALTIME REPORTER

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I N D E X

I N D E X

BE IT REMEMBERED that, pursuant to Notice, and on Monday, November 8, 1999, commencing at the hour of 9:08 a.m. thereof, at the Law Offices of Heller, Ehrman, White & McAuliffe, 333 Bush Street, Conference Room 3105, San Francisco, California, before me, FRANCES A. WEINROB, a Certified Shorthand Reporter and a Certified Realtime Reporter, there personally appeared

GEORGE KUO, Ph.D.,

called as a witness by defendants F. Hoffmann-La Roche Ltd, Roche Molecular Systems, Inc., and Roche Diagnostic Systems, Inc., and who, being first duly sworn, was thereupon examined and testified as hereinafter set forth.

THE VIDEOGRAPHER: Good morning.

This marks the beginning of Videotape 1 in the deposition of Dr. George Kuo, Ph.D., in the matter of Chiron Corporation v F. Hoffmann-La Roche Ltd, et al., in the United States District Court for the Northern District of California, Case No. 98-0315 (CW).

Today's date is November the 8th, 1999 and the time is 9:08. The location of this deposition is 333 Bush Street, San Francisco, California.

The deposition was noticed by the attorneys

for Hoffmann-La Roche Ltd, Roche Molecular Systems, Incorporated and Roche Diagnostic Systems, Incorporated, and the videotape is being produced on behalf of the same.

The video operator is Vincent Brown, a California Notary Public for the County of San Francisco, employed by Dan Mottaz Video Productions at 402 Dewey Boulevard, San Francisco, California 94116, area code (415) 731-1300.

Our court reporter today is Fran Weinrob with the reporting firm of Grossman & Cotter.

Would counsel present please identify themselves and state whom they represent.

MR. RABINOWITZ: Stephen Rabinowitz, Pennie & Edmonds, LLP for the Roche defendants.

MR. HERRIDGE: Peter Herridge, Pennie & Edmonds, LLP for the Roche defendants.

MR. PERHACS: Pablo Perhacs, Pennie & Edmonds, LLP, also for the La Roche defendants.

MR. GRECO: Richard Greco, Kay, Scholer, Fierman, Hays & Handler, LLP, for Chiron Corporation, the plaintiff.

THE VIDEOGRAPHER: If there are no stipulations at this time, may the reporter swear in

the witness.

MR. RABINOWITZ: Certainly, please go ahead.

(Witness sworn.)

EXAMINATION BY MR. RABINOWITZ

MR. RABINOWITZ: Q. Good morning, doctor.

A. Good morning.

Q. Would you please state your full name for the record.

A. Yes. My name is George Kuo.

Q. Thank you. And the pronunciation is "Kuo"?

A. That is okay.

Q. I'll try to get that right.

My name is Stephen Rabinowitz. I'll be asking questions at your deposition here today, and the questions and your answers will be recorded by Fran Weinrob, the court reporter.

I would ask you to speak up and to answer orally because the reporter can't transcribe hand gestures and nodding or shaking of your head.

Is that okay?

A. Sure.

Q. If for any reason you don't understand the question, please let me know and I'll try and rephrase it more clearly. Okay?

A. Sure.
Q. And if at any time you need a break, please let us know. We'll deal with whatever question is pending, and then we'll schedule a break as soon as possible. Okay?
A. Yes.
Q. Also, if you've given an answer and you subsequently realize that you have more information that's responsive to the question or if you need to clarify the answer you've given, please let us know and once we've dealt with whatever question is then pending, we'll deal with -- we'll give you an opportunity to clarify your answer or supplement it at that time. Okay?
A. Yes.
Q. In addition, if while you're answering a question you think of some documents that might enable you to remember information that's responsive to the question, please tell us and we'll see if we have the documents here or, if we don't have them here, if we can get them. Okay?
A. Okay.
Q. Dr. Kuo, your English is fluent, is it?
A. I guess so.

Q. Your higher education has been in English?
A. No, I educated in Taiwan.
Q. I see. You do your scientific work in English. Is that right?
A. Yes.
Q. And you write your papers, your scientific papers, in English. Correct?
A. Correct.
Q. Right. Is there any reason that you might have difficulty in understanding questions today or in answering them?
A. I don't think so.
Q. You're not taking any medications or any drug of any kind that might impair your ability to understand my questions or to answer them accurately?
A. No.
Q. No. Have you ever been deposed before?
A. Yes.
Q. In what cases have you been deposed?
A. In hepatitis C protease case.
Q. And who were the parties in that case?
A. You mean the company's name?
Q. Yes.
A. It's Eli Lilly.

Q. I beg your pardon?
A. The party is Eli Lilly -- right? -- is the company.
MR. GRECO: I think he said "Eli Lilly."
MR. RABINOWITZ: Oh, Eli Lilly.
Q. This was Chiron pursuing Eli Lilly, was it?
A. Agouron, Vertex and Gilead.
Q. So that's Chiron versus Eli Lilly & Co, right? Chiron versus Agouron?
A. Yes.
Q. Chiron versus Vertex?
A. Yes.
Q. And Chiron versus Gilead?
A. Yes.
Q. Is that G-i-l-e-a-d?
A. I think so.
Q. Right. Were you deposed once in relation to all those cases, or were you deposed more than once?
A. Only once.
Q. Once. What was the subject matter of the patents that were being litigated in that case?
A. This is hepatitis C protease.
Q. Okay. And, generally, what was the -- what

did your testimony relate to in the deposition there?
A. It related to hepatitis C protease.
Q. Did you discuss the definition of hepatitis C virus?
MR. GRECO: Object to the form.
Answer if you recall.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Did you discuss antibodies against hepatitis C virus or any hepatitis C virus peptides?
A. Yes.
Q. So you testified about antibodies to hepatitis C virus or peptides encoded by hepatitis C virus. Correct?
A. Plus something else.
Q. What else did you testify about?
A. The genome, the protein, and other things.
Q. I see. Apart from the Chiron cases involving Eli Lilly, Agouron, Vertex and Gilead, have you ever given deposition testimony in any other litigation?
A. In the United States?
Q. In the United States or elsewhere.
A. Only in -- deposition is confined in the

United States.
Q. So besides those cases, you've never given a deposition in any other case? I'll ask you separately about in-court testimony in a moment.
MR. GRECO: I think that's what the confusion is.
MR. RABINOWITZ: Yes.
Q. I'm asking specifically about depositions at the moment.
A. No, that's it.
Q. Right. Now, as for any other evidence you've given under oath besides depositions, have you ever testified under oath --
A. I don't understand your question.
Q. Have you ever given evidence in court?
A. In what respect?
Q. In any litigation at all.
A. I still don't understand the question.
Q. Have you ever testified in a court of law?
A. In relate to a patent or relate to something else?
Q. In relation to anything whatsoever.
A. No, I didn't.
Q. Have you ever been a witness in any

litigation?
A. No. I don't recall.
Q. Do you recall that Chiron was involved in a litigation against Organon?
A. That is in U.K.?
Q. In the U.K. and perhaps elsewhere.
A. Yes.
Q. Were you a witness in that case?
A. In the court, yes.
Q. Okay. Are there any --
So I'm now trying to ask about any cases, including, for example, Chiron versus Organon in the U.K. Any case in any country where you've been a witness.
A. You have to define the question clearly for me, because your question is very, very broad. So you want to relate to the hepatitis C or something else?
Q. I'm talking about relating to anything. I'm just asking you to give me a list of all the cases that you've been a witness or given testimony in, no matter what they relate to and no matter where they occurred.
A. Yes, in the U.K., yes. The Organon, yes.
Q. The Organon case.
A. Yes.

Q. Any other cases?
A. I don't recall.
Q. Would you please describe for me your educational background since high school.
A. I get my bachelor degree from National Taiwan University, and my Ph.D. from Albert Einstein College of Medicine in molecular biology.
Q. Any other formal education after high school?
A. I did my postdoc at Yale, and I work at UCSF School of Medicine before I join Chiron.
Q. And apart from National Taiwan University, Albert Einstein College of Medicine, a postdoc at Yale, working at UCSF School of Medicine, any other education after high school, or is that the lot?
A. I worked at College of Medicine, National Taiwan University after I got my bachelor degree.
Q. And anything else?
A. No.
Q. Okay. Let's go back to your bachelor's degree at National Taiwan University. What year did you begin your studies there?
A. 1957.
Q. And what year did you end your --

A. '61.
Q. Did you graduate in 1961?
A. Correct.
Q. And what was your major concentration in university?
A. In science.
Q. Did you subspecialize in --
A. No, bachelor of science.
Q. So that included physics?
A. Yes.
Q. And chemistry?
A. Yes.
Q. Biology?
A. Yes.
Q. Molecular biology?
A. No.
Q. Immunology?
A. Yes.
Q. Did you do as an undergraduate any bench work in the laboratory?
A. Yes.
Q. What projects were you involved in as an undergraduate student?
A. This relate to microbiology and immunology.

Q. What was the -- what projects did you have in microbiology?
A. Try to find out the half-life for antibiotics in rabbit.
(Reporter interruption.)
THE WITNESS: In the rabbit animal, rabbit.
MR. RABINOWITZ: Q. Any other microbiology projects?
A. That already took my whole year's work.
Q. Okay. Did you work with viruses at that time?
A. Yes.
Q. What work did you do with viruses?
A. Well, that is just in the class.
Q. And what viruses did you work with?
A. It's a medical microbiology, so cover all the biology relate to the human.
Q. I see. Did you do any experimental work with viruses at that time?
A. Experiment is doing the lab work. So I experiment.
Q. What kinds of experiments did you do that involved viruses as an undergraduate?

A. Titered, for example, influenza virus and so on.
Q. What other viruses did you work with besides influenza virus?
A. After I graduated, I worked with polyoma virus SV-40.
Q. Where was that?
A. Adenovirus.
Initial time at University Medical School.
Q. Polyoma SV-40?
A. SV-40.
Q. Right. Any other viruses?
A. Adenovirus.
(Reporter interruption.)
MR. RABINOWITZ: I think we'll have to spell them.
Q. Could you spell adenovirus?
A. A-D-N-O --
Q. Is that A-D-E-N-O-V-I-R-U-S?
A. Yes.
Q. Okay. Any other viruses?
A. I don't recall.
Q. And besides titrating antibiotics in rabbits and working with the viruses you've named, were there

any other projects as an undergraduate in microbiology?
A. You have to define the question for me and then I can answer, because this is a whole year class. So you want me to spend whole day trying to tell you -- What kind of virus do you want me to answer? You ask me question, I say yes or no. I think that is easier for me.
Q. I think it would take a very long time if we confined this to purely yes or no questions.
I'm interested in getting an overview of your exposure to bench science as an undergraduate. So you told me that you titrated antibiotics in rabbits and --
A. Textbook we use in medical microbiology is the textbook by Zinzer, so that is a very well-known medical textbook. So in there we have to learn all the virus that's in there, then we have to do some experiment.
Q. Okay, and it's the experiments you did that I'm focusing on. I'm not asking about the content of the instructional course. I'm asking about the experiments that you actually did in the laboratories while you were at --
A. Mostly I don't recall. If you ask the

simple question, I can answer it.
Q. Okay. Well, answer as far as you can recollect, and, you know, if you don't recollect anything else, then you'll just give that answer and that will be fine.
You said that you did laboratory work in immunology as an undergraduate at National University of Taiwan. What projects did you have in immunology there?
A. I tried to the get the polyclonal antibody.
(Reporter interruption.)
MR. GRECO: Polyclonal antibody. P-O-L-Y-C-L-O-N-A-L, antibody.
MR. RABINOWITZ: Q. Against what did you try and raise polyclonal antibodies?
A. This is a lot of different bacteria and virus, so I really don't recall.
Q. In what animals did you try and raise the antibody?
A. Mostly rabbit.
Q. Rabbits. Animals other than rabbits?
A. Sometime we use a guinea pig.
Q. Guinea pig. Any other animals that you can remember?

A. I don't remember.
Q. Did you use mice?
A. Rarely.
Q. Rarely. But you did use them sometimes?
A. Yes.
Q. How about rats?
A. I don't recall.
Q. Horses?
A. No.
Q. No. Did you begin work --
Did you continue working at National Taiwan University immediately after you graduated in 1961?
A. I did my military service for one year.
Q. From 1961 to 1962?
A. Correct.
Q. Did you begin working at National Taiwan University in 1962?
A. Correct.
Q. And when did you finish working there?
A. '67.
Q. What were your job titles while you were working at --
A. I was instructor of microbiology and immunology.

Q. Instructor in microbiology and immunology?
A. Correct.
Q. And you had that title when you --
That was still your title when you finished working at the university?
A. Correct.
Q. What were your responsibilities while you were working there?
A. This is two responsibility. One is research project, and other is help to teach the student. Medical student, dental student and so on.
Q. Tell me about your research while you were working at National Taiwan University. This is now as a graduate. What projects were you involved in there?
A. The big project is at that time people find the polio vaccine is heavily contaminated with SV-40, and the SV-40 has been proved to induce tumor in newborn hamster.
So people worry about if people get a polio vaccine contaminated with SV-40, eventually will get cancer or not.
So our big project is since we cannot use a human, can we use a primate, like a monkey, to do the similar experiment.

So we grow the SV-40, we get a pregnant mother monkey and we get a newborn monkey and try to inject SV-40 in the newborn monkey and try to see what kind of outcome we get.
So in order to do that, since SV-40 is the serum virus only found in monkey, but this polio virus also induce a tumor in newborn hamster and that is -- we used that as a control.
At the same time, we have to use other virus, so I work not only on this virus, we also work on polio virus.
Q. So to summarize that, would it be accurate to say that you worked with viruses including polio virus, SV-40, proteoma --
A. Polyoma.
Q. -- polyoma virus, injecting them into primates, including monkeys, as well as hamsters?
A. Right. At the same time we have to develop some tissue culture system in order to grow all these different viruses.
Q. Okay. You described that as your big project, your major project. Is that right?
A. That is clearly where the money come from.
Q. Did you have minor projects as well?

A. That is -- we have to do a lot of control.
Q. So your projects were all related to this one?
A. Correct.
Q. What did you do immediately after you left National Taiwan University in 1967?
A. I did my graduate work.
Q. When did you begin as a graduate --
A. '67.
Q. In 1967 at Albert Einstein College of Medicine. When did you finish your graduate studies?
A. In '72.
Q. Did you graduate in that year?
A. Correct.
Q. What was your Ph.D. thesis about?
A. In vitro replication of RNA virus.
Q. In vitro replication of?
A. Phage RNA.
Q. Phage RNA?
A. Correct.
Q. Sometimes it happens that students start out on one project, move to a second project, and then finally focus on a third project.
Did you have any other projects besides the

one you've just told me about?
A. No. That is only project.
Q. Can you tell me a little bit more about what that project involved?
A. We want to find a system in vitro to replicate infectious RNA, and we use the RNA phage from E. coli as the model system.
Q. Would you explain to me what a phage is?
A. Phage is the virus infected E. coli or bacteria.
Q. So this phage was an RNA virus?
A. Correct.
Q. Was it a positive-stranded RNA virus?
A. In bacteria phage, we don't use the positive strain and minor strain.
So, yes, if you can define, it have a message, messenger property. So you can say that is positive.
Q. Will you explain to me what is a positive-stranded RNA virus?
A. It's similar to messenger RNA. The genome of the cell carries the message.
Q. And if it's not positive-stranded, is it negative-stranded?

A. I guess so, yes.
Q. And would you explain to me what the difference is between them, between the positive-stranded and the negative-stranded viruses?
A. If I remember correctly from the textbook, the minor strain doesn't have the message, doesn't encode the polyprotein by itself.
You have to convert it into a positive strain in order to get that function.
Q. So a positive-stranded virus would be one where the virus nucleic acid carries the message?
A. As I understand.
Q. Going back to your Ph.D. work at Albert Einstein, did you use any molecular biology techniques at that time?
A. That is -- I got my Ph.D. in molecular biology.
Q. Ah, right. I had forgotten. Okay.
And what did you do immediately after leaving -- graduating from Albert Einstein in 1972?
A. I did my postdoc at Yale.
Q. You began at Yale in 1972?
A. Actually a little bit earlier.
Q. In 1971?

A. Oh, no, I didn't say that. You say that. I didn't say that.
Q. Well, I'm asking you.
A. That is depending on how you define it.
Q. Well, is it the case that one can divide RNA viruses into positive-stranded and other than positive-stranded?
A. But we are talking about RNA phage here, or we are talking about other thing here?
Q. I see. Does that classification not apply to phages?
A. I don't think so.
Q. I see. Okay. With respect to RNA viruses that infect mammals, say --
A. No, RNA phage doesn't infect --
(Simultaneous discussion.)
THE WITNESS: -- mammals.
MR. RABINOWITZ: Have you completed that answer?
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Thank you. With respect now to RNA viruses that do infect mammals, is it possible to divide them into positive-stranded and negative-stranded viruses?

A. '71, yeah.
Q. And when did you conclude your postdoc at Yale?
A. '78.
Q. What was your title when you began at Yale in '71?
A. It's postdoctoral fellow.
Q. And did your title change?
A. And then research associate.
Q. When did you become a research associate?
A. I don't recall. Maybe up to four years.
Q. About 1975?
A. Yes.
Q. And were you still a research associate until 1978?
A. That's correct.
Q. Would you tell me what you worked on as a postdoctoral fellow at Yale?
A. I work on the fruit fly, drosophila.
(Reporter interruption.)
MR. RABINOWITZ: Q. Is that D-R-O-S-O-P-H-I-L-A?
A. Drosophila, yeah. I can correct that later on.

Q. What did you do, what did you study drosophila to determine?
A. Try to study the development of biology.
Q. Okay. Did you work on anything else while you were there?
A. In term of organism?
Q. Besides looking at the developmental biology of fruit fly.
A. That is very broad. So you have to define your question.
Q. Did you work on a single project for the -- all the time you were at Yale as a postdoc?
A. Not a single one. There's several different projects. Try to understand how the fruit fly lay the egg, very simple egg, and then why from the egg it become the head, and the bottom of the side become wing, what controls that mechanism.
Q. But they were all in the general area of developmental biology of drosophila?
A. Yes, correct.
Q. Did you use any immunology techniques --
A. Yes, I did.
Q. What did you do with regard to immunology while you were a postdoc?

A. Try to use a polyclonal antibody to study the development of biology.
Q. What did you make polyclonal antibodies against?
A. Against some protein from the drosophila embryo or egg.
Q. Would you just explain to me what a polyclonal antibody is? It's a term that we've used without explaining up to now.
A. When you inject the antigen or immunogen into the animal, and you get a serum from animal and try to find the antibody in that serum, that more likely is a polyclonal antibody. It's a mixture of antibody.
Q. When you inject a protein into an animal, do you always get antibodies against the protein?
A. That is not always. That depend on what kind of protein you inject.
Q. Okay. Does it matter what animal you are using to inject the protein into?
A. Yes, it does.
Q. So is it the case that one animal, say a rabbit, might make antibodies against a given protein and another animal, like a horse, might not?

A. That depend how you define, so you are talking about a titre of antibody or the quality of the antibody? So that is different.
So don't say in general. You have to define for me.
Q. Does it sometimes happen that a particular animal doesn't make antibodies against a particular protein at all, whereas another animal does?
A. I cannot recall that, no. I don't think that is true statement.
Q. Well, let's take an example of porcine insulin. All right? Insulin from pigs.
A. Okay.
Q. If that were injected into humans, as happens in therapy, do you know whether you get antibodies, human antibodies against the pig insulin?
MR. GRECO: Object to the question.
You can answer. Go ahead.
THE WITNESS: To your knowledge, insulin of human and the porcine only one amino acid different?
MR. RABINOWITZ: Q. But do you know whether or not humans make antibodies --
A. Some human will because it is one amino acid different.

Q. Some humans do make antibodies against pig insulin?
A. This is what people believe.
Q. If that same pig insulin is injected into pigs, do you know whether pigs make antibodies against that insulin?
A. That is circumstantial, because that's why when you ask me about all this question. Actin from human.
If you inject into the human or into other animal, because it's a conserve, you never will produce antibody from your -- I don't say "never," but when you use conventional method to measure the antibody titre, the titre is extremely low or zero.
But if you denature the actin, inject into the rabbit, then you do make antibody.
Q. I see.
A. So same actin, same molecule. One is native and one is denature.
So if you ask the question, you have to define for me and don't give me a very broad question. I cannot answer.
Q. Okay. So do I understand you correctly to say that in order to know whether an animal will make

antibodies against a protein, you also need to know the conditions under which the protein is administered to the animal?

A. If you are using the conserve protein.

So if you inject the foreign protein to animal never sees this before, then more likely you will make antibody.

Q. Now, you mentioned whether the protein has been denatured influences the antibody response. Is that correct?

A. That's correct.

Q. What other things would influence the antibody response?

A. I think you have to rephrase the question for me, because what you are thinking may be different from what I'm thinking.

Q. You said to me that the antibody response to an injected protein would -- might depend on whether the protein has been denatured; is that accurate?

A. If you want to make antibody, I give you example like actin, then you have to denature it in order to get an antibody. So I give you this example.

If you want to ask me about other example, then you have to give me the particular. Your insulin

is a good one, but give me some example, maybe I can answer it.

Q. But as a general matter, I'm trying to elicit some general principles now --

A. In science, there's no general. So you have to --

You cannot generalize. There's a lot of things you can generalize, sometimes you cannot. There's some exception, what I try to say.

Q. Okay. Would you explain to me, please, what an epitope is?

MR. GRECO: I'm going to object to this whole line of questioning. He can answer the question, but this is, I think, A, irrelevant to the case we're litigating and, secondly, he's testifying here as a fact witness.

You seem to be very far afield from the issues in the case, but you go ahead and answer. I have my objection on the record.

THE WITNESS: Yes. As I understand, epitope is the region where bind the antibody. So that is definition.

MR. RABINOWITZ: Q. It's a region of?

A. Of peptide.

Q. So an epitope is a region of a peptide to which an antibody binds?

A. Correct.

Q. Is that the same thing as an antigenic determinant?

A. Antigenic -- I would say not exactly.

Q. What is an antigenic determinant?

A. Antigenic determinant is the region we are eliciting the antibody.

Q. So an antigenic determinant is a region of a peptide that elicits an antibody response?

A. You can say peptide, or some other thing.

Q. Of an antigen including a peptide?

A. Right.

Q. Whereas an epitope is a region of an antigen, such as a peptide, to which an antibody binds?

A. Right.

Q. Now, if I take a peptide, would insulin, human insulin, be an example of a peptide?

A. It's a polypeptide, yes.

Q. If I inject that into, say, rabbits and into horses, would the rabbits recognize the same epitopes as the horses would?

A. No.

Q. Why not?

A. You inject into the same horses, you don't get the same response.

Q. I'm sorry, would you say that again?

A. Even when you inject into the same animal, you don't necessarily get identical result.

Q. You mean into different individuals of the same species?

A. Correct.

Q. So if I inject human insulin into one rabbit, that rabbit would not in general recognize the same epitopes as a second rabbit?

A. That in general is true.

Q. And that's true for horses as well?

A. I guess so.

Q. Would that be true for humans?

A. You inject human into human?

Q. No. If I inject a protein or a peptide, a non-human protein or peptide into humans.

A. That in general is true.

Q. So different individuals of the same species do not generally recognize exactly the same epitopes on a given protein?

A. That in general is correct.

Q. Is that also true when you're comparing different species of responders?

MR. GRECO: Same objection. Again, you're getting further and further away from anything conceivably related to this case.

This is an interesting academic discussion, but he's not testifying here as an expert, and I don't see what insulin in horses has anything to do with the patents we're litigating.

I'll let you continue for a while. Go ahead.

THE WITNESS: Can you ask the question again?

MR. RABINOWITZ: Q. Yes. You've just told me that in general different individuals from the same species do not recognize exactly the same epitopes on an injected, administered antigen.

Is that also true for -- if I injected into one species compared to injecting it into a different species?

A. Okay. So here is you want to see the different, or you want to see the similarity?

Q. I'm asking whether a different species, like a rabbit versus a horse, would recognize exactly the

same epitope on a protein that's foreign to both of them.

A. No, I try to correct my answer earlier on.

If you inject into a rabbit with the same antigen, the rabbit will generally -- the antibody recognizes general epitope, but at the same time will generate different antibody.

So there's a different. There's a similarity, too.

Q. So the rabbit would recognize a variety of epitopes on the protein?

A. Right, unless there's some different -- or some will be different, some will be the same.

Q. And the horse would also recognize a variety of epitopes on the protein?

A. I never work with horse, but I guess that is generally true.

Q. But the epitopes recognized by the rabbit would not in general be the same epitopes as the epitopes recognized by the horse?

A. I didn't say that.

Q. I'm asking if that's --

A. That is not necessarily true.

Q. There might be some overlap?

A. Yes.

Q. Are there likely to be some differences?

A. That's correct.

Q. Okay. Let's go back to your postdoc at Yale. You said that you, as far as immunology is concerned, you were developing polyclonal antibodies against proteins from drosophila.

Did you have any other immunology project?

A. That is a very, very big project.

Q. I understand that, but besides that very big project, did you have other immunology projects?

A. No.

Q. What did you do immediately after leaving Yale in 1978?

A. I just state I also work with, try to find out the complexity for messenger RNA in the drosophila.

Q. Any other projects you can think of that you did while at Yale? And we're talking about in broad categories.

A. That's all.

Q. What did you do immediately after leaving Yale in 1978?

A. I come to UCSF School of Medicine department of biochemistry.

Q. Did you begin at UCSF in 1978?

A. Correct.

Q. When did you leave UCSF?

A. '81.

Q. What was your title when you began?

A. At?

Q. At UCSF.

A. Assistant research biochemist.

Q. And did you have the same title when you finished in 1981?

A. Correct.

Q. What did you do research-wise while you were at UCSF?

A. Continue very similar what I did at Yale.

Q. So you continued with the drosophila developmental studies?

A. Correct.

Q. Did you continue to raise polyclonal antibodies?

A. At that time I switched to monoclonal antibody.

Q. Did you continue to research the complexity of RNA in drosophila?

A. Correct.

Q. Did you work with viruses during this time?
A. No.
Q. Did you work with viruses while you were at Yale?
A. I don't recall.
Q. What did you do immediately after leaving UCSF in 1981?
A. I joined Chiron Corporation.
Q. Did you join Chiron in 1981?
A. Correct.
Q. What was your title in the beginning at Chiron?
A. Senior scientist.
Q. Did that title ever change?
A. Yes.
Q. When did that change?
A. I don't recall. Changed to research -- director of research, and later on changed to Chiron fellow.
Q. So you were a senior scientist, and then the next title you had was director of research?
A. Correct.
Q. And after --
A. Then Chiron fellow.

Q. The next title you had after director of research was Chiron fellow.
A. Correct.
Q. Do you know when you became a Chiron fellow?
A. '92.
Q. Do you know approximately how long after you began at Chiron you were made director of research?
A. I don't recall.
Q. Was it more than five years later?
A. Four or five years, yes.
Q. Would that be 1985 to 1986?
A. That's -- yeah.
Q. When you joined Chiron in 1981, what did you begin working with?
A. My project is the factor VIII project. Factor VIII.
Q. What did you do with respect to factor VIII?
A. Try to purify factor VIII to identify factor VIII peptide in order to sequence, then to clone the factor VIII.
Q. Okay. Were there any other projects you were working on apart from this factor VIII project?
A. Then I got involved in the hepatitis B surface antigen project.

Q. Hepatitis?
A. B.
Q. B surface antigen. When did you begin working on that project?
A. This is overlapping project.
Q. Right. So your involvement with the factor VIII project began in 1981.
A. Right.
Q. When did your involvement with the hepatitis B surface antigen project begin?
A. That is always we have very few people, so a lot of people working several different project.
Q. Did the hepatitis B project begin as early as 1981 as well?
A. Correct.
Q. Any other projects while you were a senior scientist?
A. I think that maybe that's it.
Q. When did you stop working with factor VIII, with the factor VIII project?
A. You mean stop or start?
Q. Stop. You began in 1981. When did that end?
A. I could not recall. Because this is another

overlapping project, so it's continuous.
Q. Do you continue to work with the factor VIII project today?
A. Right, so then we -- no, because we pass to other people.
Once we identify the peptide, we give the people material to sequence amino acid, once get amino acid sequence, give to the cloner to clone the factor VIII.
Q. Did you continue to work on the factor VIII project after you became a director of research?
A. I don't think so.
Q. So as far as you can remember, you stopped working on that before you became a director of reseearch?
A. That's right.
Q. And as for the hepatitis B surface antigen project, did you continue working with that after you became director of research?
A. Yes, we also involved in the hepatitis B diagnostic project.
Q. Hepatitis B diagnostic project. When did that begin?
A. I don't recall a time.

Q. Did it begin before you became a director of research?
A. Maybe a little bit earlier.
Q. And your involvement with it began around the time or a little earlier perhaps than you became director of research?
A. Right.
Q. As director of research, apart from the hepatitis B diagnostic project, what other projects were you involved in?
A. Involved in the Tumor Necrosis Factor, TNF.
Q. What were you doing with respect to Tumor Necrosis Factor?
A. We try to generate monoclonal antibody for the septic shock, or sepsis.
Q. And any other project while you were director of research?
A. No, that's almost it.
Q. So you were working on hepatitis B and Tumor Necrosis Factor factor, and nothing else as far as you can remember?
A. Right. At the same time, we --
There's only few senior scientists at Chiron, so we always have a meeting, we always discuss.

But in term of responsibilities, that maybe is my responsibility.
Q. In terms of your responsibility and your own research?
A. Correct.
Q. And as a Chiron fellow, what were you working on?
A. Right now it's hepatitis C.
Q. When did you begin working on hepatitis C?
A. That is -- now, again, your question is too broad.
If earlier on I start to discuss with Michael, collaborate with Michael, that is hepatitis C project or not?
Michael is the project leader.
Q. When you say "Michael," is this Michael --
A. Houghton.
Q. -- Houghton? When did you yourself begin doing experimental work on hepatitis C?
A. Maybe it's '85.
Q. While you were --
After you became director of research?
A. Yes.
Q. Just so that I understand correctly, you did

not do any research yourself on hepatitis C as a senior scientist?
A. But my chairman ask me to do something on the non A, non B, or hepatitis C, when I joined. So that is working on?
Because, again, your question is too vague. I cannot really answer your question.
So when we have -- '81, we have a company, we set up a project. Non A, non B hepatitis is one of the project, and my chairman ask me to get involved in that. And so I try to work to develop the monoclonal antibody.
So is that a project, or is it involved or not?
Q. Did you do any experimental work with respect to -- in response to that request by your chairman?
A. Well, I didn't.
Q. You did not?
A. Did not.
Q. Okay. When -- do you recall --
When you say your chairman, who was that?
A. Dr. Rutter.
Q. So Dr. Rutter asked you to develop

monoclonal antibodies against non A, non B hepatitis?
A. Yes.
Q. Do you recall when that was?
A. In early '82.
Q. And you did --
But, however, you did not do any experimental work --
A. That's correct.
Q. -- towards that goal?
A. Right, but we discuss the project.
Q. Did you ever do any experimental work with respect to the project you're talking about now, identified by Dr. Rutter, of making monoclonal antibodies?
A. Right now?
Q. At any time while you were at Chiron.
A. Yes.
Q. When did that begin?
A. After we clone hepatitis C.
Q. Okay. When did you --
What year, do you recall?
A. You mean the time to clone hepatitis C, or what --
Q. No, at what time did you begin working on

making monoclonal antibodies to hepatitis C.
A. After we clone the 5-1-1, we clone the C-100. We have the antigen. We decide to make a polyclonal antibody. Sometime we make a monoclonal antibody.
Not necessarily in my lab. We can send out to other outside to make it.
Q. So when did you clone hepatitis C?
A. So, again, we identify, or we --
Q. You said you cloned hepatitis C. Is that right?
A. Our group.
Q. Yes, your group cloned hepatitis C.
A. Yeah, so after we clone 5-1-1.
Q. When did that happen?
A. It is '87 we really identify.
Q. So did you yourself or anyone that you were directly supervising begin working to make monoclonal antibodies to hepatitis C proteins after 1987?
A. You mean after or before?
Q. After. I thought you told me --
Is it correct that you and the people who were working under you did not attempt to make monoclonal antibodies before 5-1-1 was cloned?

A. Because we don't have antigen.
Q. Is that correct, is that accurate, that you did not?
A. No, that's correct. But for my group, but I didn't say the other group at Chiron.
Q. Okay. But your group did not attempt to make monoclonal antibodies --
A. That's correct.
Q. -- against non A, non B hepatitis until after 5-1-1 was cloned. Right?
A. That's correct.
Q. You mentioned another group that was --
Was there a group that did try and do that?
A. I guess so, but you better ask Michael Houghton.
Q. I see. So you don't know whether or not Dr. Houghton's group was attempting to make antibodies?
A. I believe they try.
Q. Do you know whether they succeeded at that time?
A. You have to ask Michael.
When you say "succeeded," so that is also you have to define for me. "Succeed" mean a lot of different things.

I do believe they succeed to generate monoclonal antibody, but they have no way to know they have antibody. So are you going to say they succeed or they fail?
MR. RABINOWITZ: Okay. I think that's a very specific answer, which satisfies me to that question.
Would this be a good time for a break?
MR. GRECO: If you'd like, sure.
THE VIDEOGRAPHER: Going off record. Time now is 10:01.
(Recess.)
THE VIDEOGRAPHER: Going back on record. Time now is 10:12.
MR. RABINOWITZ: Q. Dr. Kuo, let me take you back to when you began at Chiron as a senior scientist in 1981. Whom did you report to at that time?
A. Dr. Pablo Valenzuela.
Q. Can you spell his name?
A. Pablo.
Q. Pablo?
A. Valenzuela, V-A-L-E-N-Z-U-E-L-A.
Q. Was he your direct supervisor?

A. He's a research director.
Q. And did you work in a group with other scientists?
A. Yes.
Q. Who else was working in your group at the time?
A. Brian Craine, C-R-A-I-N-E.
Q. C-R-E-I?
A. A-I-N-E.
Q. Anyone else?
A. That's it. He's a Ph.D. scientist.
Q. Other scientists without Ph.D.s?
A. We call research associate.
Q. Okay. Were there research associates in your group?
A. Yes.
Q. Who were they?
A. It's Won Sang Lee, L-E-E, and Carol Kuo.
Q. K-U-O, the same as the spelling of your name?
A. Yes.
Q. Besides Won Sang Lee and Carol Kuo, who else?
A. We are very small group. We work very

closely, so you have to define.

Like factor VIII project, I am in charge of purify factor VIII. Someone else is going to sequence it. Someone else is going to do the cloning. So they are all factor VIII team.

Q. But was there a formal group to which you were assigned for organizational purposes?

A. We didn't have -- everybody individual.

Q. I see.

A. At that time, everybody report to Pablo Valenzuela. So we run like a university.

Q. Whom were you working with on the hepatitis B surface antigen project?

A. That is Pablo Valenzuela's project.

Q. What other scientists were you working with on that project?

A. I just say, it's very early on. We, everybody, get involved.

Q. So you were working with Brian Craine on that project?

A. Yes.

Q. Were you working with any other scientists on that project besides Brian Craine?

When I say "scientists," I'm using it in the

sense that you used it, people with Ph.D.'s.

A. So with Pablo and with other people.

Q. What other people?

A. You have to go back to all very early on Chiron. Everybody involved. So you have to define.

I think it's difficult for me. If you name the someone, then I can answer yes, he's involved. But if you ask from the top of my head, I cannot answer.

Q. Are you saying that every single Ph.D. scientist at Chiron was involved in the hepatitis B surface antigen --

A. Very early on, everybody get involved.

Q. How many Ph.D. scientists were there at Chiron?

A. There may be only less than 20.

Q. And is it your testimony that all 20 of those were working on the hepatitis B surface antigen project?

A. Involved in it.

Q. Well, can you name some of them for me to the best of your recollection?

A. Like Graham Bell, Robert Hallowell.

Q. Can you spell that?

A. Maybe later on I can spell for you.

Q. Is that H-A-L-I-W-E-L-L?

A. Something like that, but I don't remember.

Q. Any more names you can remember of Ph.D.'s who were working on --

A. Martha Truett. Frank Majors (phonetic).

That's all I can remember.

Q. Those are all you remember?

A. Yes.

Q. Now, with respect to the hepatitis B diagnostic project, whom did you report to for that?

A. Still is Pablo Valenzuela.

Q. Were the Ph.D.s working with you on that project the same as the Ph.D.s who were working with you on the surface antigen project?

A. Actually, this is a contract research project with Lucky Goldstar, Korean company.

Q. Yes?

A. They send a lot of scientists to my lab.

Q. Can you tell me --

A. At the same time, Pablo Valenzuela and his people are also involved in this.

Q. So as far as the Chiron people were concerned, were they the same people as were working on the hepatitis B surface antigen project?

A. That's correct, and plus the people report directly to Pablo. His own group.

Q. And in addition, were there people from -- sent by Goldstar who were working on the diagnostic project?

A. Yes, the same involvement.

Q. And can you tell me their names?

A. I'm sorry, I don't recall that.

Q. You don't remember the names of any of the Goldstar scientists?

A. This, I don't remember. If you give me some time, I can write it down.

Q. Okay, that's fine. As I said to you at the beginning, Dr. Kuo, if you recall in the course of the deposition more names in response to this, just let us know and we'll give you an opportunity to mention them.

A. Sure.

Q. When you say hepatitis B diagnostic project, what did that project involve?

A. Involved develop the diagnostic test for hepatitis B surface antigen, it's anti-core, anti-e for Korean market.

Q. Were these serological tests?

A. Correct. But, again, you have to say

surface antigen is not for serological test.
Q. What test is the surface antigen test?
A. You pick up the antigen test.
Q. By means of an antibody?
A. Yes.
Q. When you were a senior scientist, how did you report to Dr. Valenzuela? Was that in written form?
A. No.
Q. Did you report to him personally?
A. If necessary.
Q. Did you make regular reports to him?
A. No. We are individual. We have 100% of freedom to do our research.
Q. So you didn't make regular oral reports to him or regular written reports to him?
A. No.
Q. Did you report any of your results at meetings, laboratory meetings?
A. Very early on, we don't have regular meeting.
Q. Did you have meetings sometimes?
A. Yes. Like we have senior scientists meeting.

Q. How often would those occur?
A. Once in two months.
Q. More or less regularly once every two months?
A. No.
Q. How many a year would you say actually happened?
A. Five or six times.
Q. What would be discussed at senior scientist meetings?
A. This project, direction of the research.
Q. Would each senior scientist at that meeting describe the direction of his or her research?
A. Yes.
Q. Would they describe their recent results?
A. If they're important result.
Q. Would they give an idea of progress in their research projects?
A. I guess so. Yes.
Q. Were minutes kept of the senior scientist meeting?
A. I don't know.
Q. Did you ever receive a copy of any minutes of a senior scientist --

A. I don't recall.
Q. Did you ever write any kind of written report at all as a senior scientist on your research?
A. In any project?
Q. In any of the projects you were doing --
A. The factor VIII project, we would write partially because there were so many people were involved.
Q. Whom did you report to for the factor VIII project?
A. Still Pablo Valenzuela.
But the project, we worked for Nordisk. Danish company.
Q. Okay. And were written reports made in the factor VIII project?
A. Yes, I think so.
Q. How often were they made?
A. That, I don't recall.
Q. On a regular basis?
A. "Regular" means? So you have to define. "Regular" means once a year or six months?
Q. Do you recall it was more than once a year?
A. I think it's maybe twice a year.
Q. Did you receive copies of those reports?

A. Yes.
Q. Would they have been circulated to everyone at Chiron, or only to some people at Chiron?
A. I would say so, yes.
Q. Do you think everyone got them?
A. Not everyone get it. People involved in the factor VIII.
Q. Okay. So all the scientists working on the project would have received --
A. Yes.
Q. When you became director of research, whom did you report to then?
A. It's Pablo Valenzuela.
Q. What was Dr. Valenzuela's title in 1981?
A. He's vice-president and director of research.
Q. Was that still his title in 1985 to 1986 when you became director of research?
A. Yes.
Q. Did you make -- as a director of research, did you make written reports to anyone?
A. No. That is just the title. Still we do the same thing.
Q. Your reporting structures didn't change when

you became director of research?
A. That's correct.
Q. Did you continue to attend the senior scientist meetings when you became director of research?
A. Then we didn't have a senior scientist meeting. Because everybody become -- title getting higher, so we have a Tuesday meeting. Tuesday seminar -- weekly meeting.
Q. When did those meetings begin?
A. I don't recall.
Q. Did they begin before you became a director of research?
A. I guess it will be around that period.
Q. What was the -- what was discussed at the Tuesday meetings?
A. Discuss our project.
Q. Was each meeting devoted to one project, or did everyone in turn --
A. Devoted to one project.
Q. Would you know before attending the meeting what project would be discussed that week?
A. Yes.
Q. How did you know that?

A. It's announcement.
Q. In what form was the announcement made?
A. Sometime we have a memo sent out say, okay, this week we will discuss this project; next week, all like that.
Q. A memo that was circulated --
A. That's correct.
Q. -- at Chiron? Who circulated the memos?
A. Pablo Valenzuela will send out.
Q. Was this Tuesday meeting limited to people working under Dr. Valenzuela, or did other people not under him also report there, their work, at those meetings?
A. Anybody at Chiron will attend if they want. So it's Chiron confidential.
Q. So anyone at Chiron could attend. Does that mean that the memos announcing the topics would be sent to Chiron broadly and not only to Dr. Valenzuela's group?
A. I think you have to appreciate, that is very small company. 80%, 90% of people are working on research.
Q. Did all the research scientists fall under Dr. Valenzuela?

A. Yes.
Q. I see. So did the hepatitis -- or the non A, non B hepatitis project fall under Dr. Valenzuela as well?
A. That's correct.
Q. So at those Tuesday meetings, did people report from time to time progress on the non A, non B hepatitis project?
A. Yes.
Q. Before you became a Chiron fellow, did you ever write written reports on your work?
A. Yes.
Q. How many times a year would you do that?
A. Only few times.
Q. A few times every year?
A. Right. But we had to write annual report.
Q. An annual report, and that accounts for one time every year. What about the other times?
A. Just as necessary. For example, we have to write a report to our Nordisk or Lucky Goldstar. Our contract research, we have to write a report.
Q. Right. For projects where you didn't have an outside collaborator, was it only the annual report that you would write?

A. That's correct.
Q. Who would receive annual reports from you?
A. It's Valenzuela.
Q. Would they be circulated to anyone else?
A. No. It's confidential. It's evaluation of your performance.
Q. Did Dr. Valenzuela alone evaluate you?
A. That, I don't know.
Q. So you don't know whether he -- whether those reports were shown to other people who were -- who may have been involved in evaluating?
A. I don't know.
Q. While you were a director of research, did you include work on the non A, non B hepatitis project in any of your annual reports?
A. Yes.
Q. Do you remember the first year in which you included such work in an annual report?
A. No, no. We are confused here.
Annual report is just performance report. It's not what you are thinking about, annual report. It's what did you do for this year.
So if for this year I write down, I say I did TNF, I did non A, non B or hepatitis C project, I

would just write down. It's not like a report.
Q. So it included experimental -- it included work that you did?
A. Yes. No experimental detail.
Q. And you did write annual reports which included information about your involvement on the non A, non B hepatitis project; correct?
A. That's correct.
Q. When was the first year in which your annual report included subject matter concerning the non A, non B hepatitis project?
A. So we are confused here.
You ask me, in general do you write annual report. I say this is for the performance, we have to write for Pablo Valenzuela or human resources. And you try to ask me when. The time, I don't recall.
But we do have a non A, non B hepatitis project report, so we will be edited by Michael Houghton.
So among those report, I will have to write small part or big part of it. That depend on how much we did in my group.
Q. So apart from your annual reports, you also prepared reports to Dr. Houghton for him to --

A. To edit.
Q. -- to edit for purposes of producing a non A, non B hepatitis report?
A. That's correct.
Q. How often did you send reports to Dr. Houghton concerning the non A, non B hepatitis project?
A. It's no regular basis.
Q. I beg your pardon?
A. There's no regular basis. When necessary, we write.
Q. Did you not make at least an annual report about work on the non A, non B hepatitis project to Dr. Houghton?
A. No.
Q. Were there some years in which you never wrote any report to Dr. Houghton?
A. Some year in '81, I didn't write. '82, I didn't write. So --
Q. What about '83?
A. No.
Q. What about '84?
A. No.
Q. '85?

A. No.
Q. '86?
A. '85-'86, maybe.
Q. Are you saying '85 no, '86 maybe?
A. No. The report you are --
Your question make me very difficult to answer.
Q. Okay. Let's try it this way.
A. So you are trying to say written report, or are you trying to say did you involve in the non A, non B hepatitis research, or discuss with that. That is different.
Q. I'm asking now about written reports. I'm asking --
I'm trying to work with you to establish the first year in which you produced a written report to send to Dr. Houghton concerning the non A, non B hepatitis project. So far you recall that you didn't do it up to 1984.
A. All right.
Q. And I'm now asking, do you recall whether you wrote such a report in 1985?
A. But as you know, I didn't report to Michael Houghton. I only report to Pablo Valenzuela, so

there's no reason I'd write a report to Michael Houghton.
Q. Dr. Kuo, you had testified that you produced written reports to send to Dr. Houghton so that he could edit them and produce a non A, non B --
A. If he ask me to put together in order for him to report to someone, I would do that.
So there's no regular basis I have to write something to him, because I didn't report to him.
Q. Now, the reports of that kind that you've just mentioned, did you write such a report in 1985 as far as you can recall?
MR. GRECO: Object to the form.
THE WITNESS: I don't recall.
MR. RABINOWITZ: Q. Did you write the report to Dr. Houghton about non A, non B hepatitis project in 1986?
A. Written report you're talking about?
Q. A written report.
MR. GRECO: Well, object to the form.
By "report to Dr. Houghton," do you mean to include something he wrote for Dr. Houghton to put into some report? Is that what you mean?
MR. RABINOWITZ: Let me rephrase.

MR. GRECO: I think that's his confusion.

MR. RABINOWITZ: Let me rephrase the question.

Q. Did you prepare any written material and send it -- for sending to Dr. Houghton concerning the non A, non B hepatitis project in 1986?

A. I don't recall.

Q. And in 1985?

A. That, I don't recall.

Q. Do you recall with respect to 1987?

A. Yes.

Q. Did you prepare written material and send it to Dr. Houghton concerning the non A, non B hepatitis work?

A. I think so.

Q. 1988?

A. Yes.

Q. And if I ask about the years subsequent to 1988, would you have done that every year until a certain time?

A. I would say so, yes.

Q. When did that stop?

A. We never stopped.

Q. It continues to this day?

A. Yes.

Q. Okay. So just to summarize, you recall that you wrote material to Dr. Houghton -- for Dr. Houghton to compile a project report concerning the non A, non B hepatitis project from 1987 and every year subsequently. Is that correct?

MR. GRECO: Object to the form.

THE WITNESS: As I recall.

MR. RABINOWITZ: Q. But you're uncertain whether you did in 1985 and 1986?

A. I don't recall.

Q. Do you know if copies of those -- of any of your written reports exist today?

A. That, I don't know.

Q. Do you keep copies of your own reports?

A. No.

Q. So you have no copies of any annual report that you wrote?

A. I don't think so.

Q. You have no copies of any written material you prepared for Dr. Houghton concerning the non A, non B hepatitis project?

A. We just move to the new building. We threw

away everything.

Q. When did that move happen?

A. Last year.

Q. When last year?

A. In July.

Q. Do you know whether there were any copies of your annual reports in your possession before you moved?

A. I didn't know.

Q. Do you know --

A. Because we moved from big office to small office, so we have to get rid of a lot of different paper.

Q. Did you review the papers before you decided -- before some of them were discarded?

A. Usually, I don't.

Q. Did anyone review them?

A. No.

Q. How many directors of research were there at Chiron when you became a director of research?

A. I don't know. I don't recall. Quite a few.

Q. More than 50?

A. Less than that. Maybe five or six.

Q. Five or six. Can you remember any of their

names?

A. Kathy Steimer, Nadine Berg (phonetic).

Any other, I don't remember.

Q. Were there any other directors of research working with the Chiron project? Working with the -- I beg your pardon, working with the non A, non B hepatitis project?

A. You better ask Michael Houghton about this. He's the project leader.

Q. As far as you can recall, do you know whether any of the people working on the non A, non B hepatitis project had the title of director of research?

MR. GRECO: At any time, or when?

MR. RABINOWITZ: At any time.

THE WITNESS: I don't remember. I think you better ask Michael Houghton. I really don't know.

MR. RABINOWITZ: Okay.

Q. So you don't know whether or not.

And then let me ask as a Chiron fellow, whom do you report to?

A. Pablo Valenzuela.

Q. What is Dr. Valenzuela's title today?

A. Senior vice-president. But this report

system is for convenience.
Q. Pardon?
A. Chiron is for convenience. Chiron fellow is a very honorary title. It is a corporate vice-president label, so theoretically we only report to the corporation.
Q. So you are a vice-president of Chiron Corporation?
A. No. The title is fairly equal to the corporate vice-president.
(Reporter interruption.)
MR. GRECO: I think he said a fellow is equal to a corporate vice-president. Is that right?
THE WITNESS: Yes.
MR. RABINOWITZ: Q. But you are not formally a vice-president of Chiron, are you?
A. No.
Q. Do you make written reports today -- or since you have been a Chiron fellow, have you continued to make written reports?
A. Only for the annual evaluation.
Q. You continue to write an annual report for your evaluation.
A. Right.

Q. And whom do you send that to?
A. To human resources.
Q. To anyone -- to any named person at human resources?
A. To the person in charge our division.
Q. Who is that?
A. Right now, we don't have any. Just left.
Q. When was the last annual report that you wrote?
A. To whom, or?
Q. No, when did you write the last annual report that you wrote.
A. This is last year.
Q. And to whom did you send that report?
A. J. Mike Smith.
Q. I'm sorry, can you say that name again?
A. Mike Smith.
Q. Let me just clear up some confusion. At some point did you send annual reports to Dr. Valenzuela?
A. Yes.
Q. Did you also send copies of those reports to human resources?
A. At that time we did not have human

resources.
Q. I see. When did you first have a human resources department?
A. I don't recall.
Q. Does Dr. Valenzuela continue --
Since you've had a human resources department, does Dr. Valenzuela continue to receive copies of your annual report as well?
A. Yes. He has to sign before he send out.
Q. Dr. Kuo, you mentioned that as a Chiron fellow you have the same rank as a corporate vice-president. Do you own stock in Chiron?
A. Yes, I do.
Q. Do you have options to purchase stock in Chiron?
A. Yes.
Q. Do you have any financial interest in the litigation between Chiron and Roche?
MR. GRECO: Object to the form.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Can you answer the question, please?
A. Define "financial interests"? If I own the Chiron, that is a financial interest? If the Chiron

stock go up? That is also --
Q. Let me clarify. Apart from your ownership of Chiron stock and Chiron stock options, other than that, do you have any financial interest in the litigation between Chiron and Roche?
A. No, I don't.
Q. Do you receive any revenue from royalties paid under the Chiron patents directed to HCV?
A. I get one dollar out of the patent. Is that revenue or not?
Q. Apart from that one dollar, do you receive any other moneys from royalties paid under those patents?
A. No, I don't.
Q. Did Chiron pay you the dollar?
A. Yes, they did.
Q. With a bank note?
A. No, it's really very old one dollar bill.
Q. Do you still have that bill?
A. I don't remember. Maybe, if I look. I don't know.
Q. Dr. Kuo, let me ask you now about some scientific terms, and I'm going to ask you to explain to me how scientists generally use these terms in the

scientific literature. This is not in relation to any particular patents.

Are you familiar with the term "viral agent"?

A. Yes.

Q. What does the term "viral agent" mean as scientists use it in the scientific literature?

MR. GRECO: You can answer.

I'm going to object, just so I don't keep interrupting you, to the general definitions of terms unrelated to the patent as beyond the scope of proper examination.

You may go ahead and answer.

THE WITNESS: Maybe you refer to the virus?

MR. RABINOWITZ: Q. I beg your pardon?

A. You're talking about viral agent.

Q. Yes. How do scientists generally use that term?

A. It's a virus, or similar to a virus.

Or is something you don't know what kind of virus it is, so it's a very general term.

Q. So let me just be sure I understand your answer correctly. A viral agent refers to any virus?

MR. GRECO: Object to the form.

Go ahead.

THE WITNESS: Yes, from my point of view, yes. You are asking my question -- you ask question to me, so my answer will be my opinion. Not general.

I don't speak for Michael Houghton or Qui-Lim Choo.

MR. RABINOWITZ: Q. I'm asking about how you understand that term.

A. Yes.

Q. So you understand the term "viral agent" in the scientific literature to refer to viruses in general?

MR. GRECO: Object to the form.

THE WITNESS: I think that is correct.

MR. RABINOWITZ: Q. So is it true that a virus can be a viral agent even if it doesn't infect humans?

A. That, I could not answer because I don't know if that is true or not. From my knowledge, I cannot answer.

Q. Well, you've just told me that viral agent refers to viruses in general.

A. But that is the operation definition.

So you are working in the medical field, you are more interested in the disease. So when people mention about viral agent, more likely is some agent cause disease.

So we are study human biomedical field here. We are not study like RNF phage or something. So viral agent more likely in medical field more likely refer to the virus cause disease.

Q. And scientists who work with phages, do they use the term "viral agent" to --

A. I don't think so.

Q. What about scientists working with animal diseases, do they use the term "viral agent" --

A. I would say yes.

Q. Let me just complete my question, if you don't mind.

Do scientists who work with animal diseases use the word "viral agent" to include viruses infecting only animals, not humans?

A. That, I don't know. I'm not in that field, so I don't know.

Q. Have you ever seen the term "viral agent" in the literature used to refer to a virus other than a human virus?

A. I don't read those magazines in general, so I don't know.

Q. Let me ask you about the term "hybridize," as applied to nucleic acids hybridizing. What does that mean?

A. That means it's the two strand on nucleic acid. They have a homology, so they tend to come together.

Q. How does that happen? What is the mechanism?

A. Through hydrogen bonding.

Q. Does that require that the sequences be complementary?

A. Some sequence should be complementary.

Q. When you say "some sequence," what do you mean?

A. Yes, it depend on what kind of condition you are doing hybridization. Condition is a stringent or non-stringent. So it's operational.

Q. So what are stringent conditions?

A. In the high-ionic strain or low-ionic strain?

Q. Okay. Under stringent conditions, are you saying that they must be completely complementary?

A. Not necessarily completely.
This hybridization, so you are using very, very long term. So give me how many nucleotide we are talking about here so I can explain to you.
Q. Oh, does it matter how many -- how long the nucleotide sequence is?
A. Of course it does matter.
Q. What difference does that make?
A. Well, that depend on how you're going to run the assay.
Q. So for a sequence of, say, 10 nucleotides, what is the difference between a sequence of 10 nucleotides and a sequence of, say, 13 nucleotides?
MR. GRECO: Object to the form.
THE WITNESS: If you run 10, the stability will be lower than the 13, in term of the hybrid.
MR. RABINOWITZ: Q. So are you saying that a sequence of 10 needs to be -- needs to have more perfect complementarity in order to --
A. No, I didn't say that. I said the stability of the hybrid will be less stable than the 13.
Q. Are hybrids more stable if they have better complementarity than if they have less complementarity?

A. That is true.
Q. And if conditions are made more stringent, does that --
Under stringent conditions, does that permit only -- does that make -- impose a requirement for greater complementarity to remain stable than under less stringent conditions?
A. In general, that is true.
Q. So would you agree that hybridization means binding of one nucleic acid sequence to another through the binding of complementary base pairs?
A. Binding? No, I will say that is --
(Reporter interruption.)
THE WITNESS: -- hydrogen binding between the two different strain.
(Reporter interruption.)
MR. RABINOWITZ: Q. So let me run this by you again. I'm going to propose this as a definition of hybridization and see whether you agree with it; or if you don't agree with it, tell me what's wrong with it.
Hybridization is binding of one nucleic acid sequence to another through the binding of complementary based pairs.

A. Through hydrogen bonding.
Q. Through hydrogen binding.
MR. GRECO: "Bonding," I think he said.
THE WITNESS: Bonding.
MR. GRECO: Binding or bonding?
THE WITNESS: Bonding
MR. GRECO: Bonding.
MR. RABINOWITZ: Through hydrogen bonding.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Must the base pairs be completely complementary?
A. No.
Q. They need not be completely complementary?
A. You can make it not completely complementary, still there's a hybrid.
Q. And you say that the conditions are important as well?
A. Right.
Q. Is there such a thing as nonspecific hybridization?
MR. GRECO: Object to the form.
THE WITNESS: That is how you define nonspecific.
MR. RABINOWITZ: Q. What do you understand

by "nonspecific hybridization"?
A. As you know, in any test there is no absolute.
Q. Right.
A. For example, like immunoassay, there is sensitivity, specificity. You want to increase the sensitivity, the specificity is become lousy. But you don't say there's no interaction. Right? So you have to define certain condition for me to answer.
Q. I'm sorry, are you saying that nonspecific hybridization can occur depending on the conditions of the assay?
A. Yes. More likely, yes.
Q. What sort of things permit nonspecific hybridization to occur?
A. Well, in the immunoassay or in the nucleic acid?
Q. No, in the hybridization of nucleic acid.
A. Because I'm not the expert in nucleic acid, so you ask me, I only can answer how much I know.
Q. To the best of your knowledge, what sort of conditions permit nonspecific hybridization to occur?
A. It's the stringency of the hybridization.
Q. And so at low stringency --

A. This tend to have more nonspecific hybridization.
Q. And how do you -- how can you tell whether hybridization is specific or nonspecific?
A. No, you have to confirm it.
Q. How do you confirm that?
A. Use alternative assay.
Q. What alternative assay?
A. That, you are asking me even the assay field. If you run the ELISA, you score a positive, then you have to confirm by another assay which is as sensitive and to confirm your assay is specific.
Q. With respect to hybridization of nucleotides, how can you tell whether hybridization that's observed is specific or nonspecific?
A. As I mentioned, I'm no expert, so I cannot answer that.
Q. You don't know that.
When you're dealing with -- you mentioned every assay has a background. When you're evaluating results in, let's say, serological assays --
A. Right.
Q. -- how do you tell whether a result you're seeing represents background or represents a specific

binding?
A. That's what I just mention. You need an alternative assay.
Q. Do you ever subtract out the background?
A. In a blood bank setting, usually you don't, because you don't want to make a risk. Even nonspecific or false positive, you still consider that is a positive. Because if you transfuse the blood into the recipient, it cause some disease, who is going to be responsible?
Q. So you never subtract background --
A. No.
Q. -- from the counts at all?
A. I think we are talking about two different things here.
I think in the blood screening tests, even there's a false positive, unless they can confirm it is really a false positive, they can assume that is a positive.
Q. Okay. When you say "a positive," do you -- what do you mean?
A. That means -- all the tests is licensed by FDA. So FDA will already approve your test. So all the tests when you score as a positive, then you say,

yes, this is a positive.
Q. So when you're looking at a result to see whether it's to be scored as positive or negative, for example, if you have radioactive counts, do you look for zero counts being negative and any counts above zero being positive?
A. No, you cannot do that, but we are talking about nobody use RIA now.
Q. Let's talk about an RIA for the moment.
RIA, does that stand for radioimmunoassay?
A. That's correct.
Q. You say that a negative result need not be zero.
A. Define the question for me. So where are we going, so that maybe I can answer the question. Because we don't use RIA in blood bank setting.
Q. I'm talking about assays in general, I'm not talking about blood banks in particular. I'm asking you --
We're talking about scoring the result as positive or negative, and I asked you whether a result must be zero in order to be scored as negative.
MR. GRECO: Object to the form.
THE WITNESS: That is not true, because

in every place there is a background.
MR. RABINOWITZ: Q. How do you determine what the background is in a particular assay?
A. In a blood bank setting, or --
Q. No, no.
A. Because I only know in a blood bank setting.
Q. All right, in the blood bank setting, how do you determine what the background is?
A. Okay. You take a few hundred so-called normal blood donor and run through your assay. And then you take an average of what kind of OD you got, and then you plus seven standard deviation or 10 standard deviation, as the cutoff.
Once you have the cutoff, you have to do all the clinical trial, then find out if that cutoff is correct.
Above the cutoff is positive or below this is a negative. So we have to confirm that. So that is you have to do the clinical trial.
Q. So let me just be sure I'm understanding your answer correctly. You have to do calibration experiments for the assay. Is that right?
A. You have to run through a lot of sample.
Q. Right. And then you determine that a

certain result, a certain number -- a certain result will be background, and then you have to work out how many standard deviations above background the cutoff will be. Is that right?

A. That's correct.

Q. Above the cutoff is positive?

A. We assume that.

Q. Below the cutoff is taken as negative.

A. Right. Then you have to do the clinical trial.

Q. But is it generally the case that you establish a cutoff, and that above the cutoff you regard that as positive and below the cutoff you regard it as negative?

A. That is immunoassay.

Q. Immunoassay. And is that the same for other assays?

A. Give me example.

Q. Hybridization of nucleic acids.

A. That, I don't know. I'm not expert in that.

Q. Do you understand what the term "Flaviviridae" means?

A. I know the term.

Q. What are Flaviviridae?

A. I would say like yellow fever.

Q. Does that include Flaviviruses?

MR. GRECO: Object to the form.

THE WITNESS: That, I don't know.

MR. RABINOWITZ: Q. Do you know whether pestiviruses are part of the Flaviviridae?

MR. GRECO: Are you talking about today, again, as of now?

MR. RABINOWITZ: Yes, as of now.

THE WITNESS: No, I think it's separate.

MR. RABINOWITZ: They're separate.

Q. Were they part of Flaviviridae at any time?

A. Earlier on, yes, I think so.

Q. Until when, as far as you know, what pestiviruses --

A. I don't know, I don't remember.

Q. Were they separated out before 1995?

A. I don't recall.

Q. Do you recall whether that happened after 1990?

A. I don't recall.

Q. But do you recall that at one time pestiviruses were considered part of Flaviviridae?

A. Very early on, yes.

MR. GRECO: Would this be a place for a break?

MR. RABINOWITZ: Let's go off the record.

THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, this marks the end of Videotape 1. Going off record. The time now is 11:06.

(Recess.)

THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, Ph.D., this marks the beginning of Videotape 2. Going back on record. The time now is 11:16.

MR. RABINOWITZ: Q. Dr. Kuo, you told me before we broke that you moved offices last year?

A. That's correct.

Q. Do you remember when in the year --

When you say last year, was that 1998?

A. That's correct.

Q. Do you remember when in 1998 you moved?

A. I remember it was more likely July.

Q. Do you think it might have been June, as early as June?

A. People move different time, so we moved more likely it's July.

Q. More likely July. Certainly not earlier

than June?

A. I don't remember.

As I recall, it is July.

Q. Okay, good. So you recall that you moved offices yourself in July 1998.

Did the whole of Chiron move offices or only part of it?

A. All the research people.

Q. All the research people together.

A. Yes.

Q. And do you know when the earliest move was for part of that research group and when the latest move was for the rest?

A. I don't know.

Q. Did any part of the research group move before 1998?

A. I don't think so.

MR. RABINOWITZ: I would like to turn now to the patents that issued to Chiron directed to HCV nucleotides and tests using HCV nucleotides.

Actually, let me mark one of them now so we know what we're talking about.

I'd like to ask the reporter to mark this as Exhibit 200.

(WHEREUPON, DEPOSITION EXHIBIT 200 WAS MARKED FOR IDENTIFICATION.)

MR. RABINOWITZ: Q. Dr. Kuo, I'm showing you now what's been marked for identification as Exhibit 200.

Do you recognize this document?

A. Yes.

Q. What is it?

A. It's like from the title.

Q. Is it Patent No. 5,714,596?

A. Yes.

Q. Are you an inventor of this patent?

A. Yes.

Q. I'd like to ask you about your involvement in the prosecution of this patent before the Patent and Trademark Office.

Did you have any role in preparing the applications from which this patent issued?

A. It's more likely done by our patent attorney.

Q. Did you play any part in preparing those applications?

A. I don't recall.

Q. You don't recall whether or not you assisted

in preparing those applications?

A. That's correct.

Q. Do you recall whether you prepared any writing for use by the patent attorney to draft the application?

A. I don't recall.

Q. Did you provide any data to the patent attorney for use in drafting the application?

A. Could you define for me the data, what "data" means.

Q. Experimental results.

A. Experimental results. No, I don't think so. I don't recall.

Q. Did you see the text of any of the applications before they were filed with the Patent Office?

A. Yes, I did, because I have to put my signature.

Q. So did you see drafts of the applications before they were submitted?

A. I think so.

Q. Were you asked to comment on the drafts?

A. Yes.

Q. Did you make any comments on the drafts?

A. I don't recall.

MR. GRECO: Is your question specifically as to this patent, or are you talking about any --

MR. RABINOWITZ: I'm talking about the application that issued as this patent, Exhibit 200.

MR. GRECO: Okay, right. Just wanted to clarify.

MR. RABINOWITZ: Q. So you recall that you were provided with a copy of the -- of a version of the application before it was filed in the Patent Office; is that correct?

A. That's correct.

Q. And you read through the --

A. Yes.

Q. -- the application before it was filed in the Patent Office?

A. That's correct.

Q. If you had seen anything that you disagreed with, would you have mentioned that to anyone?

A. Yes, I will.

Q. Whom would you have mentioned it to?

A. More likely it will be our patent attorney.

Q. Do you recall whether you did make comments

to the patent attorney?

A. I don't --

MR. GRECO: You can answer that yes or no, but don't reveal the substance of any discussions with your attorneys.

Go ahead, you can answer.

THE WITNESS: No, I don't recall.

MR. RABINOWITZ: You don't recall.

Q. Did you agree with the statements in the applications in the final form in which they were submitted to the Patent Office?

A. Yes.

Q. Did you play --

Did you provide any assistance in responding to comments by the patent examiners during the examination of this patent?

A. I don't recall I did.

Q. Did you see copies of any of the papers sent by the patent examiners?

A. I don't recall I saw that.

Q. You think you did not?

A. Yes, that's correct.

Q. Did you help prepare any of the responses that were submitted to the Patent Office?

A. I don't recall I did.
Q. In other words, you think no?
A. No.
Q. As far as you can remember, no?
Did you provide any data for submitting to the Patent Office during the course of prosecuting these --
A. I don't recall.
Q. Does that mean as far as you remember, not?
A. That's correct.
Q. Let me direct your attention to the claims of the '596 patent, Exhibit 200. In particular Claim 1 at Column 52.
MR. GRECO: 52.
MR. RABINOWITZ: You'll see that the column numbers are provided at the top of each page.
Q. Are you an inventor of Claim 1?
MR. GRECO: Object to the form. Calls for a legal conclusion.
You may answer.
THE WITNESS: Yes, I am.
MR. RABINOWITZ: Q. What about Claim 2, are you an inventor of Claim 2?
MR. GRECO: Same objection.

You may answer.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Claim 3?
A. Yes.
Q. Claim 4?
A. Yes.
Q. Are you an inventor of Claim 5?
MR. GRECO: Same objection to all of these questions.
You may answer.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Are you an inventor of Claim 6?
A. Yes.
Q. Are you an inventor of Claim 7?
A. Yes.
Q. Are you an inventor of Claim 8?
A. Yes.
Q. Are you an inventor of Claim 9?
A. Yes.
Q. Are you an inventor of Claim 10?
A. Yes.
Q. Are you an inventor of Claim 11?
A. Yes.

Q. Are you an inventor of Claim 12?
A. Yes.
Q. Are you an inventor of Claim 13?
A. Yes.
Q. Are you an inventor of Claim 14?
A. Yes.
Q. Are you an inventor of Claim 15?
A. Yes.
Q. Are you an inventor of Claim 16?
A. Yes.
Q. Are you an inventor of Claim 17?
A. Yes.
Q. Are you an inventor of Claim 18?
A. Yes.
Q. Are you an inventor of Claim 19?
A. Yes.
Q. Are you an inventor of Claim 20?
A. Yes.
Q. Are you an inventor of Claim 21?
A. Yes.
Q. Are you an inventor of Claim 22?
A. Yes.
Q. Are you an inventor of Claim 23?
A. Yes.

Q. Are you an inventor of Claim 24?
A. Yes.
Q. Are you an inventor of Claim 25?
A. Yes.
Q. Are you an inventor of Claim 26?
A. Yes.
Q. Are you an inventor of Claim 27?
A. Yes.
Q. Are you an inventor of each and every one of the claims of the '596 patent, Exhibit 200?
MR. GRECO: Objection.
THE WITNESS: Yes.
MR. RABINOWITZ: Fortunately, the other patents have fewer claims.
Q. Let me direct your -- well, attention to the '596 patent as a whole, and in particular to the word -- the phrase "other viral agents" as it appears in Claim 1. That's at Column 52, Line 11.
I beg your pardon, Line 10.
A. Okay.
Q. Does this patent define a special meaning for the term "viral agents"?
MR. GRECO: Object to the form.
THE WITNESS: Could you read back the

question for me?

MR. RABINOWITZ: Certainly.

Q. Does the '596 patent, Exhibit 200, set forth a definition of the term "viral agent"?

A. It's just the virus cause the disease.

Q. Viral agent means a virus-causing disease?

A. Or a virus that cause disease.

Q. Refers generally to viruses causing disease?

A. No, that relate to hepatitis C.

Q. I'm sorry, are you saying that in the '596 patent, the term "viral agent" means viruses causing disease?

A. Disease is hepatitis --

MR. GRECO: Let me get an objection in, please.

Object to the form of the question. Again, are you just asking him is there a definition in the spec, or are you asking him only about the claim?

I think the question's confusing when you say "in the patent."

MR. RABINOWITZ: I'm asking in the patent as a whole -- let's take the specification to start with.

Q. The specification is the portion that begins with Column 1 and ends at Column 52, Line 5.

Is there anywhere in the specification a definition of the term "viral agent"?

MR. GRECO: I object to the form. You're really asking his memory of the text of a very long patent. I don't think that's a very fair question.

You can answer it if you can remember.

THE WITNESS: Yeah, I could not -- I have to read back.

MR. RABINOWITZ: Take a look through the patent, if you wish. I'd like to know whether there is a definition of "viral agent" set forth in the patent.

THE WITNESS: In the Column 4, it's line about 20, the second paragraph.

MR. RABINOWITZ: Yes?

THE WITNESS: Yes, so they mention about the agent. Three different viruses in course of hepatitis.

MR. RABINOWITZ: Q. Is that a definition of the term "viral agent"?

MR. GRECO: Object to the form.

THE WITNESS: Well, again, don't ask me about a terminology here.

MR. RABINOWITZ: But I'm afraid I am asking

whether the patent sets forth a definition of "viral agent."

THE WITNESS: As I can understand, "viral agent" could be equal to the viruses that cause the hepatitis.

MR. RABINOWITZ: Q. So your testimony is "viral agent" means "viruses that cause hepatitis"?

A. No, that relate to the hepatitis C.

Q. What do you mean by related to hepatitis C?

MR. GRECO: Object to the form.

THE WITNESS: It have a homology to the hepatitis C sequence.

MR. RABINOWITZ: Q. Okay. Just continue. You've identified Column 4, Line 20. See if there's anywhere else in the specification that provides a definition of the term "viral agent."

MR. GRECO: You want him to read the entire patent? I mean, it's your time, but, I mean, it doesn't seem like a very productive use of it.

THE WITNESS: So as I can say, people interchange the "viral agent" with "viruses." So that depend on who is writing the patent and who is writing the article.

MR. RABINOWITZ: Q. So you're saying that

in general, people interchange the term "viruses" and "viral agent"?

MR. GRECO: Object to the form.

THE WITNESS: From my point of view, yes.

MR. RABINOWITZ: Q. And so my question is, does this patent say that the term "viral agent" is used more narrowly than that?

A. No, I didn't say that. I say the term --

The patent define very well we have hepatitis C patent. We present the sequence. Any virus relate to this sequence is hepatitis C.

That is how we define.

Q. I understand that, but I'm directing your attention to Claim 1 now in Column 52, and it says -- talks about hybridizing to the genome of hepatitis C virus or its complement relative to other viral agents.

And I'm crying to find out whether you can identify any part of the specification that defines a meaning for "other viral agents."

MR. GRECO: Object to the form.

Your question really is you're asking him to identify things in the specification. I don't see how he can do that without reading it. I mean, as many times as I've read that, I couldn't do that from

memory.

That's literally what your question is asking him, to look at the text of the patent and identify everything that might be in there that relates to that term.

MR. RABINOWITZ: Q. I'm asking if you're aware that the specification provides any definition of the term "other viral agents."

MR. GRECO: His recollection of the specification? Because he obviously has not read it sitting here today.

You could ask him if he recalls anything, that's fair, but if you want to ask him literally what's in there, he has to read it.

MR. RABINOWITZ: Q. As you sit here today --

MR. GRECO: That's fine.

MR. RABINOWITZ: Q. -- are you aware of any definition in the specification of the term "other viral agent"?

A. I just answer the same, is that I will refer to "viral agent" is equal to "viruses."

MR. RABINOWITZ: Okay. Thank you very much.

Q. Let me direct your attention to the term

"oligonucleotide" in Claim 1. That's on the first line of Claim 1.

A. All right.

Q. Do you understand what the term "oligonucleotide" means ordinarily in science?

A. Yes.

Q. What is an oligonucleotide as scientists generally use that term?

A. It's a few nucleotide put together. It's more than one nucleotide.

Q. Is there any limit on the size of an oligonucleotide --

A. That depend on how you define it. So you have to define. Is it 10 oligonucleotide, or 20 oligonucleotide?

Q. Do you understand the term "polynucleotide" as that term is used ordinarily by scientists?

A. Yes.

Q. As scientists ordinarily use the terms, is there any difference between the meaning of "oligonucleotide" and "polynucleotide"?

A. That is another operational, practical meaning.

Q. What is the operational difference between

"oligonucleotide" and "polynucleotide"?

A. Insulin is only 50 amino acid. Are you going to say that is polypeptide or are you going to say it's a protein?

Q. I'm afraid I must ask you to answer the question.

A. So that depend on how you define. Some people will say 50 is enough to call polynucleotide, but some people will say no, that is still oligonucleotide.

Q. Are you saying that in general, polynucleotides are used for bigger nucleotide -- bigger sequences?

A. Yeah, in general, that is the truth.

Q. And oligonucleotides are used for smaller sequences?

A. Yes.

Q. Is there a conventional cutoff between an oligonucleotide and a polynucleotide, in size?

A. As I understand, there is no cutoff.

Q. You mean no fixed cutoff?

A. I don't think so.

Q. Would you accept that most scientists would use -- or would you accept that scientists would use

oligonucleotide for a nucleotide sequence less than, say, 150 nucleotides long?

A. That, I just answer you earlier on. So are you going to say insulin is a protein or a polypeptide?

Q. I'm interested in what you would say, Dr. Kuo.

A. So that is also define. I think it's how you're going to define it.

So some people will say that is oligo, some people will say, no, that's a polynucleotide.

Q. Do you agree that "oligonucleotide" and "polynucleotide," as used in general, do not have exactly the same meaning?

MR. GRECO: Object to the form.

THE WITNESS: I will say that is not a general question. Exact the same? I don't say that is a correct one. You ask me absolute answer, I cannot do that.

MR. RABINOWITZ: Q. But you agree that --

A. Polynucleotide could be oligonucleotide.

But oligonucleotide, more likely people won't call is a polynucleotide.

So it's a practical.

Q. And is the reason for that that

"oligonucleotides" is a term used to refer to smaller nucleotide sequences?
A. In general.
Q. And "polynucleotides" is used to refer to larger nucleotide sequences?
A. In general, but there's no absolute cutoff.
Q. Dr. Kuo, let me direct your attention to Column 9, Line 47.
Would you read to yourself the first sentence of that paragraph.
A. Yes.
Q. Do you agree that the term "polynucleotide" as used in this patent refers to a nucleotide sequence of any length?
MR. GRECO: Object to the form.
THE WITNESS: That is defined in here.
You can set up the definitions, as I just mentioned. Oligonucleotide, some people will say polynucleotide. Polynucleotide, some people will say oligonucleotide.
But in here, you have to define it.
MR. RABINOWITZ: Q. And I'm asking you to tell me how -- what's the meaning of the term "oligonucleotide."

A. The meaning is just as printed in here.
Q. And do you agree the meaning is "a nucleotide sequence of any length"?
A. Yes, we just print it.
Q. Thank you. Let me direct your attention to Column 10, Lines 28, 29 and 30.
MR. GRECO: Look at the whole paragraph if you want. He's going to ask you about 28, 29 and 30.
MR. RABINOWITZ: Yes, of course. Read any other part of the patent that you wish to read to enable you to understand the portion I'm going to direct -- I'm directing your attention to.
MR. GRECO: He's referring to the paragraph beginning -- I guess it's the one, "As used herein"?
MR. RABINOWITZ: Yes, it begins "As used herein."
THE WITNESS: Yes, I've finished.
MR. RABINOWITZ: Q. Do you agree that the term "oligonucleotide" as used in the '596 patent refers to "a nucleotide sequence of any length"?
A. When you say "any length," such as defined in this paragraph. That is defined already here, so.

Q. That's what I'm asking you about.
A. But I cannot say "any length." It's already defined in this paragraph.
Q. And do you agree that the patent --
A. I agree with this paragraph.
MR. RABINOWITZ: I'm sorry, I'm going to ask you to let me finish the question before you answer it, and then maybe you want to wait a moment so that your attorney can make an objection if he wants to, and then we'll wait for you to finish your answer completely before we move on to the next question.
Q. Do you agree that the term "oligonucleotide" as used in this patent, refer to "a nucleotide sequence of any length?"
A. My answer is it's already defined in this paragraph. So that is the definition of "oligonucleotide."
Q. Bearing in mind that definition, do you agree or disagree that --
A. But within this paragraph --
(Simultaneous discussion.)
MR. GRECO: Wait till he finishes his question.
MR. RABINOWITZ: Q. Bearing in mind the

definition set forth at Column 10 in the paragraph beginning at Line 28, do you agree or disagree that "an oligonucleotide" refers to "a nucleotide sequence of any length"?
MR. GRECO: Object to the form.
THE WITNESS: I don't agree your "any length" question, because already defined in here.
MR. RABINOWITZ: Q. And what do you disagree about "any length"?
A. Because "any" could be you will define as one or two. So this no mention about two here. So I will say my answer still inside this paragraph.
Q. Are you saying that there's a minimum size for an oligonucleotide?
A. I will say yes.
Q. What is the minimum size for an oligonucleotide, as used in this patent?
A. This is defined in here.
Q. Well, please, tell me.
A. And then later on.
Q. So you've told me that your understanding of the term "oligonucleotide" as used in this patent, conveys that there is a minimum length in order to qualify as an oligonucleotide.

MR. GRECO: Object to the form.
MR. RABINOWITZ: Q. Is that correct?
A. I will say yes. Yes.
Q. How large must a nucleotide sequence be to count as an oligonucleotide as that term is used in this patent?
MR. GRECO: Object to the form.
THE WITNESS: I think we define in the claim here, so I cannot memorize everything.
MR. RABINOWITZ: Q. Based on Column 10, the paragraph beginning at Line 28, how large must a oligonucleotide be -- a nucleotide sequence be to qualify as an oligonucleotide?
MR. GRECO: Same objection.
THE WITNESS: We set up the upper limit here. So that is still my answer.
You try to ask me about minimum. So that is not in this paragraph, so I cannot answer your question.
MR. RABINOWITZ: Q. I'm just asking you whether there is or is not a minimum limit.
A. But in this paragraph, we didn't say there's a minimum.
Q. Okay. So do you consider that there is a

minimum in order to qualify as an oligonucleotide?
A. That is -- outside this paragraph?
Q. As the term "oligonucleotide" is used in this patent.
MR. GRECO: Object to the form.
THE WITNESS: Well, the definition of "oligonucleotide" is "more than one." So I will say more than one, people can call that as oligonucleotide.
MR. RABINOWITZ: Q. So anything from -- anything that is two nucleotides or longer can be an oligonucleotide. Is that right?
A. That is from my understanding. But your definition could be different from mine, or from -- or different from Richard's.
Q. I'm asking about the definition in the patent, the way it's used in the patent.
MR. GRECO: I'm not sure what the question is now.
MR. RABINOWITZ: Q. As the term "oligonucleotide" is used in Exhibit 200, do you agree that the lower limit is two nucleotides?
A. I will say that is correct.
Q. Is there an upper limit?
A. And that is defined in here.

Q. And what is -- what does that tell you?
MR. GRECO: Objection.
MR. RABINOWITZ: Q. Is there an upper limit or not?
A. Yeah, I don't think there is an upper limit.
Q. You think there is no upper limit?
A. No.
MR. RABINOWITZ: Counsel, just for information, I'm interested in the basis of your objection as to form.
MR. GRECO: You're asking him what terms mean in the patent, which is, as you know, a legal issue that's determined by the court based on things other than the witness's personal knowledge or personal understanding. And so when you use the term "how the term is used in the patent," that really implies that you're asking for a construction of it.
Plus it's also you're asking him what literally it says. I mean, which I think is, you know, not really a proper question for a witness.
MR. RABINOWITZ: Thank you.
Q. Let me refer you back to Claim 1, Column 52. Do you have an understanding what the term "purified preparation of an oligonucleotide" means?

MR. GRECO: Same objection.
THE WITNESS: Yes, it is a --
"Purify" means it's different from the starting material.
MR. RABINOWITZ: Q. Okay. Are there any particular criteria that have to be satisfied to make an oligonucleotide preparation purified?
A. No, different people can have different standard.
Q. So if I have a preparation of an oligonucleotide and I'm trying to determine whether it falls within the scope of this claim or not, do you agree that it must be purified, at least in the meaning of this patent, before it can qualify -- before it can fall within the scope of Claim 1?
A. You have to --
MR. GRECO: Objection. Go ahead.
THE WITNESS: Sorry. You have to read the whole sentence. You cannot take half the sentence and try to ask me question.
MR. RABINOWITZ: Q. Read the whole sentence then.
A. Yes. So your oligonucleotide got to purify is not like original, and then the oligonucleotide is

capable of selectively hybridizing to the genome of the hepatitis C virus.

So that is a whole sentence.

Q. Have you completed your answer?

A. Yes.

Q. So if I have an oligonucleotide preparation that does satisfy all the other requirements of the claim, do you agree that it must be purified in order to fall within the scope of this claim?

MR. GRECO: Object to the form.

THE WITNESS: So then you have to define "purify" for me, then I can answer.

MR. RABINOWITZ: Q. Do you have an understanding of what "purified" means in this claim?

A. Yes.

Q. What does "purified" mean --

A. It means away from the starting material.

Q. Dr. Kuo, let me just restate the question because I think you began answering before I'd quite finished.

What does "purified" mean in this claim?

MR. GRECO: Same objection.

THE WITNESS: It's different from the starting material.

MR. RABINOWITZ: Q. And does that mean that any difference between the oligonucleotide and the starting material will suffice to make it purified?

A. So we're talking about oligonucleotide here. Okay? Oligonucleotide, if you synthesize it chemically from four different bases, so that is the starting material. And when you synthesize it, then if you do anything to be different from the starting material, that is purification.

Q. Okay. Is it possible to make a purified preparation of an oligonucleotide from naturally occurring sources?

A. Yes, I will guess so. This is from the nature source, yes.

Q. And what must you do to make it -- to qualify as purified if you're doing it from natural sources?

A. Define the nature source for it.

Q. How about naturally occurring hepatitis C virus?

A. Then you separate, you have to separate the protein from the nucleic acid, and that is a purification.

Q. So if it is separated from the proteins,

then it's purified?

A. I didn't say -- proteins is one of the example. You give me an example, I tell you.

Q. Okay. My example is --

A. If virus, then I say it is separate from the nucleic acid from the protein.

Q. My example is, the oligonucleotide is separated from the proteins of the hepatitis C virus. Is that purified?

MR. GRECO: Object to the form.

You may answer.

THE WITNESS: You give me the hepatitis virus. I say that is one of the purification.

MR. RABINOWITZ: Q. So that would be purified?

A. I would say yes, in my own definition.

Q. Let me direct your attention to the term "selectively hybridizing" in Claim 1 of the '596 patent.

A. Yes.

Q. Do you understand what that term means?

A. Yes.

Q. What does "selectively hybridizing" mean in Claim 1 of the '596 patent?

MR. GRECO: Objection. You may answer.

THE WITNESS: Will hybridize to the hepatitis C genome.

MR. RABINOWITZ: Q. Have you completed your answer?

A. Yes. Or it complementary related, just the whole sentence.

Q. I'm sorry, just would you tell me again what "selectively hybridizing" means?

A. To genome of hepatitis C virus or its complement relative to other viral agent.

Q. And what does that mean?

A. That means it's either hybridized through hepatitis C genome or its cDNA, for example, that is complementary or as a viral agent.

Q. So are you saying that any oligonucleotide that hybridizes to HCV or its complements will selectively hybridize within the meaning of this claim?

MR. GRECO: Same objection. Go ahead.

THE WITNESS: Yes, I think so, yes.

MR. RABINOWITZ: Q. In order for an oligonucleotide to qualify as selectively hybridizing to the genome of a hepatitis C virus or its complement, must the sequence of that oligonucleotide be the same

as hepatitis C virus or its complement?
A. That is not -- you don't have to be 100% complement.
Q. Right.
A. You say "same." You have to define for me what "same" means.
Q. Is there a minimum percentage identity that it must satisfy?
A. No. We didn't say that.
Q. So how does a scientist tell whether an oligonucleotide is capable of selectively hybridizing to a hepatitis C virus or complement?
A. Yes, your oligonucleotide will hybridize to hepatitis C or its complement.
Q. And is that sufficient to show that it selectively hybridizes --
A. Yes, under certain condition, the hybridization will occur.
Q. What does "relative to other viral agents" mean with respect to selective hybridization in this claim?
MR. GRECO: Same objection.
THE WITNESS: That means any other viruses will still hybridize.

MR. RABINOWITZ: Q. You say the oligonucleotide will hybridize to other viruses as well?
A. I didn't say that. I say when the oligo will hybridize, the nucleotide will hybridize to the hepatitis C or the complementary or as a virus agent.
Q. So are you saying it is necessary to do a comparison between hybridizing to HCV and hybridizing to other viral agents?
MR. GRECO: Object to the form.
THE WITNESS: No, I didn't say that.
MR. RABINOWITZ: Well, then, I'm afraid I don't understand your answer.
Q. I'm asking you whether there is a test one can do to determine whether an oligonucleotide is capable of selectively hybridizing to the genome of an HCV or its complement relative to other viral agents.
Do you know of such a test?
A. If the test -- what kind of test? Give me example of other tests.
Q. I'm asking you whether you know of a test one can do.
A. No, there's so many tests, so how can I answer?

Q. Well, name one.
A. Blood sample, for example. Sample from the blood bank.
Q. How would you go about testing whether an oligonucleotide satisfies this?
A. Yes, you can extract the nucleic acid and do the hybridization and then see if there's -- if any genome or nucleic acid will hybridize to this oligonucleotide.
Q. And if it does, does that show that the oligonucleotide is capable of selectively hybridizing to HCV or its complement relative to other viral agents?
A. Yes, if there is HCV there, I think the oligonucleotide will hybridize it, and that is a selectively hybridize.
MR. RABINOWITZ: I'd like to go off the record.
THE VIDEOGRAPHER: Going off record. Time now is 12:02.
(Discussion held off the record.)
(Luncheon recess: 12:02 p.m.)

AFTERNOON SESSION
(1:03 p.m.)
THE VIDEOGRAPHER: Going back on record. Time now is 1:03.
MR. RABINOWITZ: Q. Dr. Kuo, let me direct your attention back to Exhibit 200, the '596 patent, Column 19, Line 44 to 53.
And I'm still asking with respect to the meaning of "capable of selectively hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents."
Will you read that section to yourself?
MR. GRECO: Could you state the lines again, please? Column 19?
MR. RABINOWITZ: Yes, Column 19, Lines 44 to 53.
THE WITNESS: To this spot?
MR. RABINOWITZ: Q. Have you had an opportunity to read that paragraph?
A. Yes, I did.
Q. Now, turning back to Claim 1 in Column 52, does that clarify the meaning for you of "capable of selectively hybridizing to the genome of a hepatitis C virus or its complement relative to other viral

agents"?

MR. GRECO: Object to the form.

THE WITNESS: So what is your question again?

MR. RABINOWITZ: Q. Does the paragraph in Column 19 that you've just read explain the meaning of "capable of selectively hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents"?

MR. GRECO: Object to the form.

THE WITNESS: Explain partially.

MR. RABINOWITZ: Q. What does it explain about that meaning?

A. That under this condition, can the probe selectively hybridize to hepatitis C.

So this is another operational. If it doesn't, then you have to change. So the most important thing in here is the hepatitis C virus genome.

MR. RABINOWITZ: I see.

THE WITNESS: So if you want to detect the virus, if under certain condition it doesn't selectively hybridize, then you have to find a way. But still it still bond to it, I will say yes.

MR. RABINOWITZ: Q. So how do you tell when you've achieved conditions which -- under which selective binding takes place?

A. That is you have to do the clinical trial.

Q. You have to do a clinical trial?

A. Yes.

Q. And until you've done a clinical trial, it's not --

A. No, you confirm by other, by other means. This region, you have a question, then you can always use the other region to do it.

Q. So, again, you identified two ways now I think in which you say one can determine whether you have conditions which permit selective hybridization.

Firstly, you say you can do a clinical trial. Is that right?

A. Oh, if you want, yeah. If you can -- you want to do it -- how good your assay is, you can run a lot of different sample.

Q. And short of a clinical trial, how else could you determine whether you have found conditions under which the hybridization is selective to HCV relative to other viral agents?

A. You can use --

Genome is very long, about 10kb, so you can have a lot of different region to confirm that if this region doesn't selectively hybridize, or you have question about selectivity, then you can always use other region to do it.

Q. And so you say, we must do it by trial and error?

A. Not necessarily trial and error. You have the sequence in your hand, so it's not trial and error here.

Q. So how does one determine which part of the HCV genome sequence you selectively hybridize?

A. You can look at the sequence and then make a judgment.

Q. And how do you make that judgment?

A. Well, as I mentioned earlier on, I'm not an expert in the nucleic acid, so what I answer to you is from my opinion. So there's a lot of different way to do it.

Q. And in your opinion, what is one way of doing it?

A. Yeah, you just use other region to confirm. If you find something bind to one region, do you see another one to bind another region?

So, give you example, like hepatitis B surface antigen test. Why is it called sandwich assay? You ask the same question two times.

One monoclonal antibody are bind to the surface antigen. You ask another antibody, does this antibody bind to the surface antigen.

So that is in general practice.

Q. Let me direct your attention to Column 28, Lines 4 through 19.

A. Yes.

Q. Again, with respect to Claim 1, does this section that you just read explain the meaning of "capable of selectively hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents"?

MR. GRECO: Objection.

You may answer.

THE WITNESS: As I just mentioned, I'm no expert in the PCR or other things. This is just very simple description of one of the way to detect the hybridization.

MR. RABINOWITZ: Q. So that shows a way of detecting hybridization?

A. One of the way. There are several ways to

do it, so this describes one way to do it.
Q. Does this way described in Column 28, Lines 4 to 19, help you to determine whether the binding is selective or non-selective?
MR. GRECO: Object to the form.
THE WITNESS: Well, your so-called selective, you have to confirm it one way or the other. So without confirming it, so I -- I just cannot answer your question.
MR. RABINOWITZ: Q. So --
A. They say, yes, use this condition, we are selectively hybridizing. That is my answer.
Q. So do I understand correctly that you say that if you find binding, you will need to do further experiments to determine whether -- to confirm whether it is selective or not?
A. If necessary. But you cannot say there is no binding.
MR. RABINOWITZ: I'd like to ask the reporter to mark a document. I think we are up to 201 now.
(WHEREUPON, DEPOSITION EXHIBIT 201 WAS MARKED FOR IDENTIFICATION.)
MR. RABINOWITZ: Q. Dr. Kuo, I'd like to

direct your attention to the document that has been marked Exhibit 201.
Have you ever seen this document before?
A. The whole document?
Q. The whole document or any part of it.
A. I don't recall I see this.
Q. Can I ask you to turn to the second page from the top, the one that's marked with Page No. 1 on the bottom.
Can you read the title that's underlined and in bold about one-third of the way down the page?
MR. GRECO: Why don't you just read it.
MR. RABINOWITZ: Q. Do you agree that this is entitled "Declaration of William J. Brammar under 37 C.F.R. Section 1.132"?
A. Yes. I see it right now.
Q. And do you see that there's a date written in hand towards the top, 7/9/96?
A. That's correct.
Q. I'd like to direct your attention to Page 3, Paragraph 5 of the declaration.
A. Which paragraph?
Q. Paragraph 5. Would you read that to yourself, please.

And please read that and anything else in the declaration that you need to read to understand it and then let me know when you've had an opportunity to do that.
A. Okay.
Q. Have you had a chance to read the paragraph and the rest of the declaration?
A. Yes.
Q. Now, turning to Paragraph 5, Dr. Brammar says:

> Under (sic) "conditions of gradually increasing stringency, you would expect readily to find conditions under which the oligonucleotide remains hybridized only to the HCV RNA. If such a condition does not prevail, then the oligonucleotide does not selectively hybridise to the HCV genome."

Do you see that passage in Paragraph 5?
A. Yes, I do.
Q. Do you agree with that statement?
MR. GRECO: Object to the form.
Go ahead.
THE WITNESS: Partially.

MR. RABINOWITZ: Q. What do you agree with?
A. Because this is like a test tube experiment here. It's all very theoretical.
If you have something you want to hybridize it, then if you don't see the hybridization or you don't have the specificity, you try to change the condition in order to see this hybridization.
So this is based on very theoretical situation. So it's test tube, generally try to test -- generate a test tube result.
Q. And you said that you agreed with it partially. Does that mean that you partially disagree with it?
A. Yes, I partially. If you are doing, like you synthesize the oligonucleotide, you want to do some Tm or do some experiment, nothing to do with a disease, I would say this is okay. Your interest is in the Tm or the hybrid, for example.
Q. When you say "Tm," do you mean --
A. Melting temperature.
Q. Melting temperature.
A. So if you are doing physical biochemistry and started a nucleic acid, then, yeah, I agree this is the one way to do it.

Q. And what do you disagree with?
A. If you are dealing with virus agent or some infectious agent which cause human disease and then you want to develop the assay for it, for example, hepatitis C, you want to develop the screening method for hepatitis C, this maybe is not the proper way to do it.
Q. What are the limitations of this method of doing it?
A. Well, because this is based on just one hybridization. So if this fail, virus, as I mention, is 10kb, you can always use other region to do it.
Q. So in your opinion this is not a reliable way of determining this?
A. I didn't say that. I said depend on what you want to do.
Q. Do you agree that if you do not find conditions under which the oligonucleotide remains hybridized only to the HCV RNA, then the oligonucleotide does not selectively hybridize to the HCV genome?
A. That is also is operational definition. Doesn't hybridize is different meaning. So different depend on how you -- what kind of condition.

that has been placed in front of you.
Have you ever seen this document before or any part of it?
A. I don't recall.
Q. Do you see that on Page 1, the document has been labeled "Amendment"?
A. Yes.
Q. And that a date has been written in by hand, February 27, 1995?
A. Yes.
Q. And do you see that in the -- about one-third down the first page, there's written "Serial No. 08/040,564"?
A. Yes.
Q. Would you turn to the last page. Do you see that under the signature there's written the name Kenneth M. Goldman?
A. Yes.
Q. Do you know who Kenneth M. Goldman is?
A. Used to be a patent lawyer at Chiron.
Q. I see. I'd like to direct your attention to Page 11. There are three points marked in bold with bullets next to them. The second bullet point, would you read that to yourself, please.

If you have the right condition, then it will hybridize it. If you have no right condition, it won't hybridize.
Q. So do you mean that unless you specify the conditions, this isn't meaningful?
MR. GRECO: Object to the form.
THE WITNESS: Well, this is just sort of very general description. Gradually increasing stringency condition. What that means? Didn't mention anything.
So you can find a way to see the hybridization, you can find a way you don't see the hybridization. So doesn't mean it's not selectively hybridizing, so that is my answer to this.
MR. RABINOWITZ: Q. So in your view what should have been specified here to remedy --
A. I don't know. I'm not an expert witness to write this, so I really don't know. I have no opinion.
MR. RABINOWITZ: I'd like to ask the reporter to mark this next document as document 202.
(WHEREUPON, DEPOSITION EXHIBIT 202 WAS MARKED FOR IDENTIFICATION.)
MR. RABINOWITZ: Q. Dr. Kuo, I'd like to direct your attention to a document marked Exhibit 202

A. Yes.
Yes.
Q. Now, do you see that your -- the Chiron attorney has said:
"the oligonucleotide is present in an amount capable of selectively and detectably hybridizing to the genome of a hepatitis C virus HCV (or its complement) relative to other viral agents..."
Citing Page 13, Lines 3 to 19 of the '714 application, and then says it discloses:
"...that the nucleic acid contains a sequence that is identical or complementary to the HCV genome (i.e., hybridizes to the genome or its complement), and is unique when compared to other viral agents, which can be determined using hybridization to detect (or determine) whether the nucleic acid hybridizes selectively to HCV."
Do you agree with that statement?
MR. GRECO: Object to the form.

THE WITNESS: Yes.
MR. GRECO: Object also as taking out of context of what that is. I don't think it's something you can agree or disagree with.
THE WITNESS: I agree with this statement.
MR. RABINOWITZ: Q. Do you agree that for an oligonucleotide to selectively hybridize to a genome of an HCV or its complement relative to other viral agents, that it must contain a sequence that is identical or complementary to the HCV genome?
THE WITNESS: Could you read back the question?
(Record read.)
THE WITNESS: I don't agree, what you are just saying. You don't need 100% complementary.
MR. RABINOWITZ: Q. What percentage complementarity do you need?
A. That depend how long oligonucleotide you are using.
Q. Do you agree that for an oligonucleotide to be capable of selectively and detectably hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents, that the

oligonucleotide must contain the sequence that is unique when compared to other viral agents?
MR. GRECO: Object to the form.
THE WITNESS: That is -- "unique" also is relative term. So it's not absolute terminology.
"Unique" means it's relative compared with other.
MR. RABINOWITZ: Q. Well, do you agree that the oligonucleotide must contain a sequence which is unique when compared to other viral agents?
A. Not necessarily. I just mention could be it's very similar, or there's partially complementary to it.
As I just mentioned, hybridization is based on hydrogen binding and hydrogen binding is not absolute. Same as when you have antibody bind to the epitope. There's no such thing as absolute. You can have change in affinity, but antibody still bind to it.
Q. Have you completed your answer?
A. Yes.
Q. So you disagree --
A. I disagree.
Q. -- with that statement?
A. No, your statement.

MR. RABINOWITZ: Let me have marked Exhibit 203 for identification.
Excuse me, can I just take a look at that. I just want to be sure that this isn't a marked-up copy.
(WHEREUPON, DEPOSITION EXHIBIT 203 WAS MARKED FOR IDENTIFICATION.)
MR. RABINOWITZ: Q. Dr. Kuo, have you seen this document before?
A. Yes, I did.
Q. What is this document?
A. It's the patent application for the recombinant non A, non B virus polynucleotide.
Q. Now, going back to Exhibit 202, Page 11, the second bullet point refers, in the third line, to Page 13, Lines 3 to 19 of the '714 application.
Do you see that on Exhibit 203 there's a number been stamped on the first page on the top?
I'm directing you now to Exhibit 203, the top page. The first page of 203. Do you see the number 122714?
A. Yes.
Q. Will you understand if I refer to this as the '714 application, that I'm referring to

Exhibit 203?
A. Okay.
Q. If you could turn to Page 13 and read to yourself Lines 3 to 19.
MR. GRECO: Well, I think that's a paragraph that begins on the bottom of Page 12, so I think --
MR. RABINOWITZ: And anything else in that application --
MR. GRECO: I think he should at least read the full paragraph.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Does the paragraph you've just read in Exhibit 203 teach an oligonucleotide that is capable of selectively hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents?
MR. GRECO: Objection.
THE WITNESS: Just give you the example. Stable way to do it, but not the only way to do it.
MR. RABINOWITZ: Q. Does it teach the idea of an oligonucleotide that is capable of selectively hybridizing to an HCV or its complement relative to other viral agents?

A. Again, I think it says you are define selectively and detectably hybridize. So you have to define your criteria for me in order for me to answer.
Q. Well, I'm asking you whether you can find in this paragraph teachings that convey to you the idea of selectively hybridizing to HCV relative to other viral agents?
A. It's a certain way, yes, you can do it.
Q. Will you point out to me the parts of this paragraph that teach that?
MR. GRECO: Object to the form.
THE WITNESS: I just mention there's a lot of just known technology in here. For example, you can use a Tom Maniatis --
(Reporter interruption.)
THE WITNESS: You can use the textbook edited by Tom Maniatis.
MR. GRECO: "Tom Maniatis" I think he's saying.
MR. RABINOWITZ: That's M-A-N-I-A-T-I-S.
Q. Is that the reference to Page 13, Line 20?
A. No, it says 1982.
Q. Are you referring to Line 20 on Page 13 there?

identify particular sentences in that paragraph which teach the idea of an oligonucleotide that is capable of selectively hybridizing to HCV relative to other viral agents?
MR. GRECO: Objection to the form.
THE WITNESS: Well, whole paragraph already describe a lot of different thing. It's in this paragraph.
And why you ask me, say, okay, you identify. It's already described here. This whole paragraph.
You compare with the Genebank, doing some of the -- compared to the run sequence of other virus agents. Then you can do different thing. Determine complementary by known in art and discussed in Tom Maniatis.
So mismatch of duplex can treat with S1 nuclease. So that is already tell you a lot.
MR. RABINOWITZ: Q. The reason I'm focusing on this paragraph is that in Exhibit 202, the Chiron patent attorney argued that this paragraph taught the idea of an oligonucleotide that was capable of selectively and detectably hybridizing to the genome of a hepatitis C virus or its complement relative to other viral agents.

A. Line 20.
Q. Okay. Apart from Line 20, is there any other part of that paragraph that conveys the idea of an oligonucleotide capable of selectively hybridizing to HCV or its complement relative to other viral agents?
A. As I just mentioned earlier, I'm not a nucleic acid expert here, so when I read this, I would say, yes, partially will tell you how to do it.
But I'm not doing it, so I cannot answer -- really answer your question.
Q. So I'm asking you to identify for me the -- or read to me the sections that convey that idea.
A. As I just say, I'm not an expert. If you are asking me about protein chemistry or immunoassay, I can tell you, but here is -- all are in nucleic acid testing. So really I'm not in a position to answer your question.
Q. Well, are you saying that you're unable to identify --
A. Not unable, but I think if you --
MR. RABINOWITZ: I'm sorry, let me finish my question.
Q. Are you saying that you are unable to

And the Chiron patent attorney focused on a teaching that the nucleic acid contains a sequence that is identical or complementary to the HCV genome.
Now, do you see on Page 13 at Line 3, the sentence that reads:
"In addition, the sequence of the region from which the polynucleotide is derived is identical to or complementary to a sequence which is unique to the NANBV genome"?
MR. GRECO: Object to the form of that question, among other things. I also object to the characterization of the patent attorney's amendment and what he was saying there. But I'm not sure you have a question at the end of that long recitation.
MR. RABINOWITZ: Will you read back the question at the end of that long recitation.
(Record read.)
MR. RABINOWITZ: Q. Do you see that sentence, Dr. Kuo? The sentence beginning on Page 13 of Exhibit 203, Line 3, "In addition." One word in to Line 3.
A. So what is your question?
Q. So taking that sentence together with the

sentence -- the two sentences beginning on Line 11, "The sequence can also be compared to the known sequences of other viral agents, including those which are known to cause hepatitis," and he gives some examples. "The correspondence or non-correspondence of the derived sequence to other sequences can also be determined by hybridization under the appropriate stringency conditions."

Taking that portion of this paragraph, does that, taken together, convey the idea of an oligonucleotide that is capable of selectively hybridizing to HCV or its complement relative to other viral agents?

MR. GRECO: Objection.

THE WITNESS: Yes, I still believe it is capable of selectively and detectably hybridizing to a genome of the hepatitis C virus.

MR. RABINOWITZ: Q. And that's conveyed by paragraph -- this paragraph on Page 13 of Exhibit 203? Right?

A. This is one way to prove it.

Q. And is one way to prove it, hybridizing it under appropriate stringency conditions?

A. Yes. That is, yes.

Q. And are you looking for an oligonucleotide that under stringent conditions will hybridize to HCV and will not hybridize to other viruses?

MR. GRECO: Object to the form.

THE WITNESS: Again, we are not talking about absolute here. I think we are talking about relative hybridization here.

Under this condition that your oligonucleotide hybridize to hepatitis C, same time we hybridize hepatitis A or hepatitis B. Very simple question. So if the answer is no, then you find other way to do it, but doesn't mean it's not selectively hybridized to hepatitis C.

MR. RABINOWITZ: Q. But if it selectively hybridizes to hepatitis C, then it ought to hybridize to hepatitis C and not to hepatitis A. Is that right?

A. There is no such thing as absolute in biological system here, sir.

Q. And is that why you disagreed with Professor Brammar's statement in Exhibit 201?

A. I didn't disagree. That is one way to do it.

But what we are doing is biomedical research here. We are not dealing with theoretical biochemistry

here.

Q. Let me read again from Exhibit 201, Paragraph 5.

MR. GRECO: 201.

MR. RABINOWITZ: Exhibit 201, Paragraph 5.

> Under (sic) "conditions of gradually increasing stringency, you would expect readily to find conditions under which the oligonucleotide remains hybridized only to the HCV RNA."

That's on Page 3, Paragraph 5.

Do you have it there?

A. Yes.

Q. > Under (sic) "conditions of gradually increasing stringency, you would expect readily to find conditions under which the oligonucleotide remains hybridized only to the HCV RNA. If such a condition does not prevail, then the oligonucleotide does not selectively hybridise to the HCV genome."

MR. GRECO: I think you have to keep reading. To be fair, you have to read the whole context there.

> MR. RABINOWITZ: "As a negative control, one would use an oligonucleotide of the same length in base-composition, but with a randomized or scrambled sequence, and perform a parallel hybridization to a similar panel of nucleic acids."

Q. Is it wrong to say that you would expect readily to find conditions under which the oligonucleotide remains hybridized only to the HCV RNA?

A. As I say, Dr. Brammar just keep his opinion about ideal situation here. So he doesn't consider in the blood bank setting or in the laboratory setting. This is theoretical approach.

He is partially right, he is partially wrong, as I can see it.

Q. And let me just ask you the same thing about the continuation.

> "If such a condition does not prevail, then the oligonucleotide does not selectively hybridise to the HCV genome."

Do you consider that to be partially right and partially wrong as well?

A. That is my answer.
MR. RABINOWITZ: Thank you, sir.
Q. I'd like to take you back to Exhibit 200, the '596 patent, and I'm going to ask you to explain to me what the term "hepatitis C virus" means in this patent.
A. In general?
Q. In this patent, and I'm going to direct your attention to Columns 6 through 8 of Exhibit 200, the '596 patent.
MR. GRECO: Wait. Now I'm not sure what your question is anymore.
MR. RABINOWITZ: I'll restate the question.
Q. Let me direct your attention to those columns of the patent first.
MR. GRECO: All right. You want him to look at Columns 6 through 9.
THE WITNESS: So what is your question?
MR. RABINOWITZ: Q. My first question is whether you've had an opportunity to read Columns 6 through 8.
A. That too long for me to read. I think maybe better you ask a question one by one.
MR. GRECO: If you ask your question

first, then he can speed up the reading
MR. RABINOWITZ: Maybe we'll be able to focus it a little bit.
Q. Firstly, when you and your co-inventors filed the applications that issued as this patent, did you consider that hepatitis C virus included hepatitis A virus?
A. No.
Q. Did you consider that hepatitis C virus included hepatitis B virus?
A. No.
Q. Did you consider that hepatitis C virus included hepatitis D virus?
A. No.
Q. Did you consider that hepatitis C virus included hepatitis G virus?
A. There is no such thing as hepatitis G. It just is a virus looking for the disease, as you know. It doesn't cause the hepatitis.
Q. Is there such a virus that is sometimes called hepatitis G virus?
A. Eventually, if someone abandons that, I think.
Q. But is there a virus that some scientists

refer to as hepatitis G virus?
A. I guess.
Q. Did you consider that virus to be included within your understanding of hepatitis C virus?
A. We defined hepatitis C virus with this definition.
Q. I'm just asking about your understanding. Did you understand that hepatitis C virus included what is sometimes called hepatitis G virus?
A. As you know, the reason people call non A, non B hepatitis is because this is hepatitis, and when you test with hepatitis A and hepatitis B, there's no marker. So any hepatitis is not caused by A, not caused by B, it's called non A, non B hepatitis.
And later on people find hepatitis delta and hepatitis E. And that is not our patent here. We define hepatitis C in certain way. So we already put a frame there. So this is the frame we claim, this is hepatitis C.
Q. So is it accurate that you did not consider hepatitis C to include what is now called hepatitis E?
A. No. We don't think so.
Q. And did you consider that hepatitis C includes what is now called hepatitis G?

A. As I say, G is not cause hepatitis.
Q. So it doesn't include that virus?
A. I would say no.
Q. Are you familiar with a virus called BVDV?
A. Yes.
Q. Did you consider that hepatitis C virus includes BVDV?
A. We only consider human disease here.
Q. So does that mean you did not consider hepatitis C virus to include BVDV?
A. That is caused the bovine disease.
Q. Is it correct that you did not consider hepatitis C virus to include BVDV?
A. Well, I think that is in general we consider that. We only deal with human disease here.
Q. Is that a "Yes," you did not consider it to include BVDV?
A. That, I think so, yes.
Q. I have a finite list of viruses, so we'll get through to the end of them. I just want to confirm, is it true that you did not consider hepatitis C virus to include West Nile virus?
A. Well, are we sit here to test my virology knowledge, or we are defending the patent? I think,

sir -- sir, I think, sir, we are wasting time here.

Q. I'll go through this as quickly as I can. I have a few more questions of this kind and then we'll go back to the patent.

A. Because if you ask my virology knowledge, I learned it 20, 30 years ago. I really cannot answer you. I think that is --

Q. Dr. Kuo, if you don't know the answer to a question --

A. No, but it is unfair for you to ask me in here to -- why me I cannot answer it. That is not --

I'm not coming here to take a medical board, for example. Is that fair?

MR. GRECO: I think maybe you just need to clarify. When you're asking "does it include," I think the confusion may be are you asking is it related, or is it something of that nature?

MR. RABINOWITZ: Let me clarify the question in case there's any misunderstanding.

Q. I'm trying to identify what you and your co-inventors considered in your minds that what you are now calling hepatitis C virus would include and would not include. And to help define the boundaries of that, I'm trying to ask whether it -- whether your

idea, as you conceived hepatitis C virus, included particular other viruses.

And that's why I'm asking whether hepatitis C virus, as you envisioned it, would or would not include certain other viruses.

This is certainly not a test of anyone's virological knowledge, and I'm quite sure you've forgotten much more virology than I will ever know. But it's helpful to us for the purposes of this litigation to clarify what you and your co-inventors in your own minds considered that hepatitis C virus either did include or did not include.

A. That's fair.

Q. And it's with that focus that I'm asking these questions. And I know it's a little tedious and I'm going to go through this as quickly as I can, and I promise you there's a finite number which will help us identify what you and your co-inventors considered to yourselves that your hepatitis C virus covered, and then once we've done that, we'll move on.

So let me just ask again, as you and your co-inventors conceptualized hepatitis C virus, did you consider that it included West Nile virus?

A. We only deal with the virus, or viruses. At

that time, we didn't know how many viruses called non A, non B hepatitis. It caused human disease, infect the human liver, and that is what we define.

So it is the hepatitis virus, and then we call that is C. So we defined for the kind of genome we are dealing with, so that is our territory here.

Q. Is it correct that West Nile virus was identified at the time that you discovered hepatitis C virus?

A. I don't know.

Q. I see. Were you aware of yellow fever virus at the time that you discovered hepatitis C virus?

A. Yes.

Q. Did you and your co-inventors consider that hepatitis C virus should include yellow fever virus?

A. My question for you, does yellow fever cause hepatitis?

Q. Is that your answer?

A. Yes. Because you have to tell me, does that cause hepatitis or not.

Q. Let me ask the question again. I'm trying to identify whether when you were -- whether the way that you envisioned hepatitis C virus, you intended to include yellow fever virus within that name of

hepatitis C virus.

A. From my recollection, yellow fever virus doesn't cause hepatitis, so we didn't -- I don't think we would intend to include that.

Same as Epstein-Barr virus cause hepatitis, but that is DNA virus.

Q. So the Epstein-Barr virus is not within hepatitis C virus?

A. No.

Q. Nor is HIV?

A. No.

Q. Nor is herpes simplex virus?

A. We rule that out. That is when people working on non A, non B hepatitis, herpes sometimes cause hepatitis. So that is we know of.

In the field, people already automatic rule this out.

Q. So in your mind, hepatitis C virus did not include herpes simplex?

A. I don't think so.

Q. Nor human papilloma virus?

A. I don't think so.

Q. Nor -- I'm not sure whether we covered it, nor yellow fever virus?

I'm sorry?

MR. GRECO: Did you ask him that already?

MR. RABINOWITZ: I'm not sure whether we got a clear answer for the record, so let me restate the question.

Q. Just to clarify, you did not consider that hepatitis C virus as you are naming it included yellow fever virus?

A. That is my opinion. What I answer here is my opinion. One of the inventor. You have to ask the other three. Other two, not three.

Q. But in your opinion, it did not include yellow fever virus?

A. Right.

MR. RABINOWITZ: Thank you. Is this an appropriate time for a break?

MR. GRECO: Uh-huh.

THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, this marks the end of Videotape 2. Going off record, the time now is 2:03.

(Recess.)

THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, this marks the beginnng of

Videotape 3. Going back on record, the time now is 2:14.

MR. RABINOWITZ: Q. Dr. Kuo, let me draw your attention once again to Exhibit 200, which is the '596 patent, and I'm going to be asking you for the next little while about the meaning of hepatitis C virus.

Can I ask, the way hepatitis C virus is defined in this patent, is it confined to hepatitis C virus HCV-1?

A. No.

Q. It includes other strains of hepatitis C virus?

A. You mean a strain, what that means?

Q. Other isolates of hepatitis C virus.

A. I think so.

Q. So it's broader than HCV-1?

A. Because this is RNA virus, so RNA virus tend to mutate. So we say this is the virus related to this type of first isolate and cause the same disease. That is our definition.

Q. So HCV-1 was the first isolate, but your definition of HCV-1 includes other isolates as well?

A. That's correct.

Q. Does HCV-1 include only isolates isolated by 1990, which was when the application was filed, or does it include isolates discovered afterwards as well?

MR. GRECO: Object to the form.

You said HCV-1 or HCV?

MR. RABINOWITZ: HCV.

MR. GRECO: Just HCV. I thought you said "1" in your question there.

MR. RABINOWITZ: I better repeat the question just in case I did.

Q. Does the definition of HCV in the patent include only isolates of HCV that were discovered up to 1990, or does it include isolates of HCV that were discovered afterwards as well?

MR. GRECO: Object to the form.

THE WITNESS: Personally, I will say we are including the future isolate. Without our sequence, nobody can isolate the other.

MR. RABINOWITZ: Q. So your definition includes isolates found after 1990, does it?

A. Yes. And the people accept that, use the same terminology, too.

Q. Let me direct you to Column 6, Line 62. Do you see there where it says:

"The term HCV also includes new isolates of the same viral species"?

A. Right.

Q. What is a viral species?

A. That is a virus species that relate to hepatitis C.

Q. Are there criteria for determining whether one virus and another virus are members of the same species?

A. Then you have to define a species for me, because that is --

What we try to say is we have a prototype or a type 1 sequence, and we believe this is the cause of hepatitis C. And so if someone isolate another isolate, also cause the hepatitis C and it has got the same gene organization, then we will say that is the hepatitis C.

Q. Does the term "hepatitis C virus" in your patent only include viruses that cause hepatitis?

A. From my thinking, yes.

Q. So if I'm trying to classify a virus to see whether it falls within hepatitis C virus or not, do I have to establish that it causes hepatitis before I can classify it as an HCV?

A. Well, that is --
You are doing experiment. You try to do it, so that is your decision, not my decision.
Q. I'm asking -- I'm trying to establish what tests a virus must pass to be considered an HCV within the meaning of the patent. I'm asking, is one requirement that it must cause hepatitis?
MR. GRECO: Object to the form.
You may answer. Go ahead.
THE WITNESS: In here we also describe the defective virus particle, and are you going to tell me the defective virus particle of hepatitis C is not hepatitis C?
MR. RABINOWITZ: I'm actually going to ask you.
Q. Is a defective particle of hepatitis C --
A. I will say yes, because they have the same genome organization, so some reason it's defective.
Q. Do defective interfering particles cause hepatitis?
A. From definition, it's no.
Q. So does it follow that the definition of hepatitis C virus includes viruses that do not cause hepatitis?

A. The "defective particle" is operational terminology here. When you say is it defective, for you? Not necessarily defective if you inject that to me. So "defective" is a different meaning, and we think that defective virus particle is a nucleic acid; that could be infectious.
So it's the definition is an operational definition.
Q. So I'm not quite clear that I understand your response to the question whether in order to pass, to qualify as a hepatitis C virus, as the term is used in the patent, whether a virus must cause hepatitis or whether it need not cause hepatitis.
MR. GRECO: Object to the form.
You may answer.
THE WITNESS: That, I -- if you ask my opinion, I just described to you. The defective particle you find in your body is still is the virus.
You know, when you isolate the purified virus polio, only 10% are infectious, 90% defective in general. So are you going to say that defective is not a polio virus? Still, it's the polio virus.
So certain way you can define. Okay, if you isolate nucleic acid from defective particle, do they

have the same -- very similar sequence to the hepatitis C? If the answer is yes, then it's hepatitis C. If they have the same genome organization, then obviously, yes, it's hepatitis C.
MR. RABINOWITZ: Okay.
Q. Let me direct your attention to Column 6, the very last sentence beginning on Line 66.
Do you see that it says, "The terms non A, non B hepatitis and hepatitis C may be used interchangeably herein"?
A. Right.
Q. Does the "term non A, non B hepatitis" include hepatitis D?
A. No.
MR. GRECO: Objection.
Go ahead, you can answer.
MR. RABINOWITZ: Q. Is hepatitis D not a non A, non B hepatitis?
A. It's already named hepatitis D.
Q. Is that included within non A, non B hepatitis?
A. No, hepatitis D discovered after B.
The reason called non A, non B is you don't -- there's no marker for A, no marker for B, so

there's a blank there. And then later on people find hepatitis D, and hepatitis E. So --
Q. So what is the meaning of the term "non A, non B hepatitis"?
A. Well, that is just in general. In the early Seventies and middle of Seventies, when you have a test of hepatitis A and B.
Q. What does "non A, non B" mean then?
A. It's not A, not B.
Q. Does that include hepatitis D?
MR. GRECO: Objection. As to when?
THE WITNESS: That time, maybe. But as you know, hepatitis D --
How much do you know about hepatitis delta?
MR. RABINOWITZ: We're not going to explore my knowledge at this deposition. I'm just going to ask you some questions.
THE WITNESS: Because hepatitis delta is hepatitis D surface antigen.
So when you assay with the hepatitis B test, it will fall into the B. So not a B, not A is called non A, non B.
MR. RABINOWITZ: Q. Does non A, non B include hepatitis E?

MR. GRECO: Say that again, please?
MR. RABINOWITZ: Q. Does non A, non B hepatitis include hepatitis E?
A. We define in here very narrow. It's the blood-borne hepatitis. It's not A and not B. And we call, when we isolated the genome, then we named hepatitis C. So that is all.
Q. But I'm asking you about the term "non A, non B hepatitis." Does that include hepatitis E?
MR. GRECO: Objection.
THE WITNESS: That is -- as I said, we didn't use that term. That has been used by the hepatologist.
MR. RABINOWITZ: Q. You do understand the meaning of the term "non A, non B hepatitis"?
A. Yes.
Q. And are you able to tell me whether it includes hepatitis E or not?
A. Right now, it's not.
Q. At any stage, did non A, non B hepatitis include hepatitis E?
A. When people isolate hepatitis E, they find out that is not -- they didn't call hepatitis C. They call hepatitis E.

Q. But was that virus included in the general term "non A, non B hepatitis" at any time?
A. I don't think people use -- include that.
Q. Are you familiar with a virus called GBVB?
A. Yes. Not "familiar." I know this term.
Q. Would that be included within the term "non A, non B hepatitis"?
A. Does that cause virus -- cause disease?
Q. I'm asking for, in your opinion, is GBVB included in the term "non A, non B hepatitis"?
MR. GRECO: Objection to the form.
THE WITNESS: If the sequence is very similar, there's a homology; and if we can pick up with the assays basically for hepatitis C, then we will say that is part of C.
MR. RABINOWITZ: Q. And do you know whether it is part of C?
A. No, it doesn't pick up by our immunoassay, so I don't think that is included.
Q. And are you saying that hepatitis C is the same as non A, non B hepatitis?
A. Blood-borne.
Q. Blood-borne.
A. Yes.

Q. Are there forms of non A, non B hepatitis that are not blood-borne?
A. People believe so.
Q. What viruses cause --
A. The so-called community-acquired non A, non B hepatitis.
Q. And what viruses cause community-acquired non A, non B hepatitis?
A. Right now it's caused by the same virus. So although it's called "community-acquired," actually it's transmit by the blood product.
Q. So are you aware of any viruses that cause non A, non B hepatitis except for hepatitis C?
A. That is different from hepatitis C, then they should use other nomenclature.
Q. So as far as the scientific literature is concerned --
A. Yeah, they will say non A to G, or non A to F, or something.
Q. Does the scientific community identify viruses other than hepatitis C as non A, non B hepatitis viruses?
MR. GRECO: Objection.
THE WITNESS: No, they call non A to E or

non A to G, or something. That's why you have a hepatitis G. Hepatitis F has been named by the virus in mid-1990.
MR. RABINOWITZ: Q. Is hepatitis F a non A, non B hepatitis viruses?
A. It's not part of our non A, non B here. We don't define that. We define our non-hepatitis C very clear. Positive strain RNA virus cause hepatitis.
Q. I understand you've defined what hepatitis C is, but I'm asking whether the term "non A, non B hepatitis" includes hepatitis F?
A. Again, I just want to answer your question clearly. The reason they call non A, non B is if you don't have a hepatitis A marker, you don't have a hepatitis B marker, and the hepatologists just threw in the garbage can and call it non A, non B hepatitis.
So it's not our terminology.
Q. Does hepatitis F have a hepatitis A marker?
A. Hepatitis? It disappear. Once someone claim, but no longer exists.
Q. So hepatitis F is not hepatitis A. Right?
A. I don't think so.
Q. Hepatitis F is not hepatitis B?
A. I don't think so.

Q. So doesn't it follow that hepatitis F is part of that, what you've described as the garbage can non A, non B hepatitis?
A. That --
MR. GRECO: Objection.
Go ahead. You can answer.
THE WITNESS: It's a mixture.
But when we work on this project, we don't know how many viruses we are dealing with. We clone one of the virus. Then later on we find out this virus cause 90 or 95% of the so-called non A, non B hepatitis.
MR. RABINOWITZ: Q. Do you know what causes the other 5 to 10%?
A. Other virus.
Q. What are the other --
A. Maybe. We don't know.
Q. But some viruses?
A. Maybe, or unknown reason.
Q. Let me direct your attention to Column 7, the first sentence, which says:
"HCV is a viral species of which pathogenic strains cause blood-borne non A, non B hepatitis."

Are there non-pathogenic strains of hepatitis C virus?
A. So you consider defective particle is not pathogenic, or no?
Q. Would you say that the defective particle is non-pathogenic?
A. I would say neither. I will not answer, say absolutely it is not pathogenic, but I will not say it is pathogenic.
As I mentioned, if you isolate nucleic acid, that could be infectious.
Q. What is an attenuated strain?
A. That is like when you take a polio, as an example. Sabin polio strain is attenuated.
Q. What does "attenuated" mean?
A. Well, "attenuated" is English. I give you example like polio. Sabin virus is attenuated virus.
Q. And what enables it to be classified as attenuated, what properties mark a virus as attenuated?
A. If you take a polio example, that means it doesn't cause disease.
Q. Okay. So an attenuated strain is a strain that doesn't cause disease?
A. But that -- hold onto that. One of the few

hundred thousand in some people still cause disease. So are you going to say that is not pathogenic?
Q. I'm interested in your opinions.
A. No. This is science, there is no absolute. So I just want to tell you, don't force me to give you zero. There's no such thing.
Sabin is very safe vaccine, been used on million, million people. But some people do pick up the disease. In Daly City, just south of San Francisco, there's one case.
Q. So you say that --
Are you able to say whether an attenuated strain of HCV would be pathogenic, or are you saying that you can't say one way or the other?
A. I cannot say one way or the other.
Q. Okay. Let me direct your attention to Column 7, the sentence beginning on Line 8, "Therefore."
A. "Therefore." Yes.
Q. Do you see it says:
"...there are multiple strains/isolates, which may be virulent or avirulent, within the HCV species."
What does that mean?

A. Again, someone write a patent, so if you ask my opinion, I think that is -- I can explain to you, but not necessarily it's the correct answer.
Q. Well, please explain.
A. Take hepatitis C as the case. People infected with the C will recover, maybe 20%. 80% will become chronic. Among those chronic patients, some are healthy carrier. The liver function is normal. But if you detect the nucleic acid as a marker, you do detect that. But some patient will have abnormal liver function, ALT will jump up and down.
So my interpretation will be the one they call virulent form is cause the disease. But that is not absolute. Virulent strain of this infect to other people, may become avirulent.
Q. Does "avirulent" mean it doesn't cause disease?
A. Not necessarily doesn't cause disease, cause mild disease.
So, again, like Sabin virus as example. The virus duplicate. Still in your immune system. So you cannot say virus didn't replicate in the vaccinee. It does.
Q. Okay. Let me draw your attention to the

sentence beginning at the end of the third line of Paragraph 7 -- of Column 7.

"As shown infra, the HCV genome is comprised of RNA."

A. Which line?

Q. Line 3 to 4, Column 7.

A. So we're back again. Okay.

Yes.

Q. Is it -- in order to classify a virus as an HCV virus, must it have an RNA genome?

A. So you are talking about the virus exists in the nature, or nucleic acid generate in a test tube?

Q. I'm talking about the virus.

A. Yes, I will assume that is true.

Q. What I'm trying to discover is, are there a number of tests or a number of criteria that the virus must satisfy so that we can classify it as an HCV within the meaning of the patent.

And so I'm going to be going through here trying to identify what a virus must be or must look like, or must possess in order to qualify as an HCV.

A. I understand that. And also my -- I try to explain a lot of different thing even outside this patent to you so I make myself clear.

Q. Well, clarity is very good. So we'll do it in as much detail as it needs to be clear.

But, sir, you agree that to classify -- to classify a virus as hepatitis C within the meaning of the patent, it must be an RNA virus?

A. Yes.

Q. You agree it need not cause disease?

A. That is a question mark, as I just explain to you. It doesn't cause disease in you, not necessarily in other people.

Q. But you wouldn't look for proof that it causes disease in order to label it as an HCV?

MR. GRECO: Objection to the form.

MR. RABINOWITZ: Q. Is that right?

A. But as I just mentioned, are you going to do the experimental transmit to other people to prove it causes the disease, or just take one; look, we have RNA virus here, and he is healthy, there's no disease, and so it's not hepatitis C?

I say no, I don't accept that.

Q. So you're saying evidence of disease would not be necessary?

A. That's correct.

Q. Let me direct you to -- well, let me ask

you, as HCV is defined in this patent, is it necessary for a virus to be a positive-stranded RNA virus to qualify as an HCV?

A. We also cover complementary.

Q. I'm talking about the virus now. Would one have to show that it is a positive-stranded RNA virus to satisfy the definition that's set forth here?

MR. GRECO: Object to the form.

THE WITNESS: I think so. But also we have to define very clear the sequence gene organization.

MR. RABINOWITZ: Q. We'll get to that in a while. I'm just trying to find out whether positive strandedness is a criterion for being a hepatitis C virus.

You say it is a criterion?

A. Right.

Q. Let me draw your attention to Column 8, Lines 14 to 15. It says:

"In addition, it is believed that the genome would be a positive-stranded RNA."

A. Yes.

Q. Some of the statements in the patent are

prefaced by words like "it is believed" or "it is expected."

Does this mean -- "it is believed," does this mean that it is a necessary property of the HCV genome?

MR. GRECO: Objection to the form.

THE WITNESS: You better ask our attorney. This is a legal terminology, so I cannot answer your question.

MR. RABINOWITZ: Q. When you read it yourself, do you understand whether it's necessary or not necessary for an HCV to have a positive-stranded RNA genome?

MR. GRECO: Objection.

THE WITNESS: It's one of the criteria, not the only criteria.

MR. RABINOWITZ: Q. So you're saying it must have a positive-stranded RNA genome?

A. But a positive strand doesn't have a coding sequence, doesn't have a nucleatized sequence, a homology to hepatitis C. So I don't think that is the criteria. So it's one of the criteria.

Q. So it's one of the criteria?

A. Yes.

Q. I'm now going to ask you about amino acid homology to the HCV-1 amino acid sequence.

I'm going to direct your attention to Column 8, the first paragraph, beginning on Line 1 and ending on Line -- I believe it's 15.

Please let me know when you've had a chance to read that paragraph.

A. Yes.

Q. Let me read you the first three sentences. It says:

"Different strains, isolates or subtypes of HCV are expected to contain variations at the amino acid and nucleic acids compared with HCV1. Many isolates are expected to show much (i.e., more than about 40%) homology in the total amino acid sequence compared with HCV1. However, it may also be found that there are other less homologous HCV isolates."

Is there a threshold amino acid homology with HCV-1 that is required to be classified as an HCV?

MR. GRECO: Objection to the form.

THE WITNESS: No, I don't think so. This

is just arbitrary number.

MR. RABINOWITZ: Q. And is it your view that a virus can be an HCV even if it's less homologous than 40% at the amino acid level?

A. That depend on which part of the polypeptide you want to compare. You are going to compare the conserve region, or compare with the envelope region?

So if you compare with the envelope region, you may be able to find more than 40% difference.

Q. Well, the sentence, "However, it may also be found that there are other less homologous HCV isolates" --

A. Right.

Q. -- does that indicate that a virus can qualify as an HCV even if it's less homologous than 40%?

A. You're playing a number here. I think we have to look at the function of this virus.

If this virus got the same property, cause the disease and have a certain region, is a conserve, for example, a nucleocapsid region, and there's some protease region, because those are important for the virus, they are conserved. The other particle could be mutant, could be different, but cause the same disease

and get the same genome organization, I will say that is hepatitis C.

Q. Okay. Now, going back to that second sentence in Paragraph 8, it says:

"Many isolates are expected to show much (i.e., more than about 40%) homology in the total amino acid sequence compared with HCV1."

Do you agree that's talking about overall homology in the total amino acid sequence of the one virus compared with -- of the candidate virus compared with HCV-1?

A. Yes, I agree, from the region here, yes.

Q. And then it says:

"However, it may also be found that there are other less homologous HCV isolates."

Does that indicate that a candidate virus might classify as an HCV on other criteria, even if it's less than 40% homologous in the total amino acid sequence to HCV-1?

A. But you have to read further. You cannot take from the context and ask me the question.

Could you just read further up, and then you

answer to yourself.

Q. That's why I say "might" qualify based on other criteria. I'm just trying to find out --

I'm going to take one criterion after the other and ask whether it's essential. Now, you've testified that it's essential that it be an RNA virus; it's essential that it be a positive-stranded virus or an A virus; it's not essential that it cause disease.

Right?

A. In certain condition.

Q. Now I'm trying to find out whether it's essential that it must be at least 40% homologous at the amino acid level.

And based on what is said here, I'm asking whether you agree, it need not necessarily be 40% or more homologous in the total amino acid sequence to HCV-1.

MR. GRECO: Objection to the form.

THE WITNESS: I could not answer your question, because it is confusing for me here, so I don't know.

MR. RABINOWITZ: Okay.

Q. Then it says:

"These would be defined as HCV

according to various criteria..."

Now, do you agree that the word "these" is referring to "other less homologous HCV isolates?"

A. Don't ask me the English -- the attorney's English here. I just don't understand your question, so I'm sorry.

Q. Okay. Well, can you tell me what you understand by the rest of the paragraph beginning "These would be defined" and ending at the end of the paragraph?

MR. GRECO: Objection to the form.

THE WITNESS: It says, open reading frame of approximately 9,000 nucleotide to approximately 12,000 nucleotide, encoding a polyprotein similar in size to that of hepatitis HCV-1.

So then you define an encoded polyprotein of similar hydrophobic or antigenic character to that of HCV-1.

So do I have to do it?

MR. RABINOWITZ: Q. Well, let's take them -- and then it also says:

"...and the presence of co-linear peptide sequences that are conserved with HCV1."

Right?

A. Right.

Q. Okay, let's take them one by one.

An open reading frame of approximately 9,000 nucleotides to approximately 12,000 nucleotides.

What does "approximately 9,000 nucleotides" mean?

MR. GRECO: Objection.

THE WITNESS: It's just English.

MR. RABINOWITZ: Q. Does that mean plus or minus 25% or 50%, or how much variation is "approximately"?

A. No, don't ask me that kind of question. I don't know. It's approximate. It's English defined here. So don't ask me to pin down. I could not answer your question.

Q. And would that be the same if I asked you "approximately 12,000 nucleotides" --

A. Oh, yes. I will say yes, I could not answer.

Q. What is a polyprotein similar in size to that of HCV-1? What does that mean?

MR. GRECO: Objection to the form.

THE WITNESS: That means the gene

organization encoded a different gene, and that gene could be approximate, could be longer or could be shorter.

MR. RABINOWITZ: Q. What does "similar in size" mean? Again, how similar does it need to be?

MR. GRECO: Objection.

THE WITNESS: As we discover in this patent, we are dealing with RNA virus. RNA virus tend to mutate. There is no proof reading for this virus.

So even one virus infect you, if I isolate the virus from you, you are going to -- we are going to see thousand different kind of sequence.

So that is how we say, okay, approximate. So I cannot tell you exact number. Few amino acid, I could not tell.

MR. RABINOWITZ: Q. Do you know what the size is of the HCV-1 polyprotein?

A. This is about 3,000 amino acid.

Q. 3,000 amino acids?

A. Right.

Q. So based on that, are you able to give me any boundaries for how similar -- how long or short a protein -- a polyprotein would be that was similar in size to the one of HCV-1?

A. No, I cannot.

Q. Okay. The next one says, an encoded protein of similar hydrophobic and/or antigenic character to that of HCV-1.

What does it mean, "similar hydrophobic character"?

MR. GRECO: Objection.

THE WITNESS: It's hydrophobicity profile of the polyprotein.

MR. RABINOWITZ: Q. And how does one determine whether something is similar to, in hydrophobicity, to HCV-1 polyprotein?

A. You just run the computer program with your amino acid sequence, and then you find out the hydrophobicity profile and you can compare one isolate from other isolate, do you see the very similar profile.

Q. Are there numerical scores for similarity?

A. No numerical score for hydrophobicity -- hydrophobicity.

Q. Is that the kind of thing one has to compare by eye?

A. No, you can put on the computer, and then it will draw the graph for you.

Q. And do you have to compare the two graphs by eye to see how similar they are, or are there algorithms for determining the --

A. You can decide by your eye. You can tell by your eye, but if you are fancy, you can go into the computer to tell you.

Q. So are there computer algorithms for measuring the similarity or dissimilarity of hydrophobicity of different proteins?

A. Yes.

Q. Were -- in 1990, were there such programs available?

A. I think so, yes.

Q. Were there many different programs?

A. That, I don't know.

Q. And what's the meaning of "an encoded polyprotein of similar antigenic character to that of HCV1"?

A. That, as I read this, if you express the protein, the protein will pick up the antibody against HCV-1.

Q. Which antibody is that?

A. The antibody against HCV-1 will react with your tentative antigen. If you isolate -- when you

isolate, you express in E. coli yeast or mammalian cell, get the protein out, ask very simple question. Does this protein react with patient infected with hepatitis C, type 1? So is there any cross-reaction.

Q. So you'd rely on samples of -- on serum samples from patients to determine similarity?

A. Not necessarily patient. You can get rabbit serum or goat serum, if you inject HCV-1 antigen into the animal.

Q. So if you have a candidate virus and you want to see whether its encoded polyprotein has similar antigenic character, you would express the polyprotein, and test it with a serum, say a rabbit serum, against HCV-1 to see whether the serum binds?

A. Right.

Q. And if the serum binds, that would show that the polyprotein has similar antigenic character?

A. Yes.

Q. So are you saying that any cross-reactivity between the polyprotein and the HCV-1 polyprotein shows similar antigenic character?

MR. GRECO: Object to the form.

THE WITNESS: So can you read back?

(Record read.)

THE WITNESS: Your question is too broad for me to answer.

MR. RABINOWITZ: Q. In what respect is it too broad?

A. Because you try to say cross-react is absolute number?

Let me answer differently. All immunoassay used worldwide is based on hepatitis C, prototype 1. And they perform very, very well. There's no instance of non A, non B hepatitis in this country and in Japan and Europe. And if you isolate in here, in Europe, in Japan, there's a different isolate.

So what I try to answer intellectually is there is a cross-reaction.

So you can express the other isolate into the protein and ask question, say, that's an antibody against HCV-1 cross-react. And then alternative is patient infected with, select, say, genotype 2 cross-react with protein of HCV-1. That is another way to do it. And the answer is, yes, I will say both will react.

Q. Okay. Now, what I'm trying to clarify is, when the patent says "similar antigenic character" --

A. Right.

Q. -- does that mean that you only -- that you need only have, say, one antiserum that recognizes both proteins, or must many different antisera recognize both proteins?

MR. GRECO: Objection to the form.

THE WITNESS: You are dealing with a polyclonal antibody here. Right? So the antibody only recognize five amino acid.

So if the antibody against this five amino acid -- against this five amino acid, what are you going to say?

So, I don't know, I think that is -- I try to answer it, say most or almost all the isolate will tend to have very similar protein. And if infected in the patient, we are still making the same kind of antibody, that's why when we use the type 1 HCV, the common antigen will pick up all the different isolate in the world.

So I think that is the best I can answer to you.

MR. RABINOWITZ: Q. Isn't it true that hepatitis C virus shares some antigenic determinants with some Flaviviruses?

A. You consider Dengue is Flavivirus or no?

Q. I'm willing to go with your characterization. Do you consider Dengue a Flavivirus?
A. We tested very early on. We get a sample from Trinidad, which is heavily infected with Dengue. We didn't see any cross-reaction.
But I will not say absolute. There's no such thing in the test as a zero and a something. We are not dealing with computer here. So what I try to say is statistic.
Q. But are you aware of any cross-react --
A. Our test is doing very well worldwide, so if there's a cross-reaction, our test will be rejected.
Q. I'm not confining it to your tests. I'm talking about considering all the antigens on HCV and all the antigens on Flaviviruses, is there any common antigen between HCV and any other Flavivirus that you're aware of?
A. Well, that -- the best method is epidemiology. If the test is used in million, million people, what else you can get best example?
So maybe we are coming to different place, so I don't know how to answer your question.
Q. Dr. Kuo, I'm not confining my question to your test. Isn't it true that your test measures --

How many different HCV antigens does your test measure?
MR. GRECO: Objection to the form.
THE WITNESS: No, we are measuring antibody.
MR. RABINOWITZ: Q. Antibodies to how many different antigens in HCV?
A. We use a core, and there's three, and there's four, and it end at five.
Q. Four antigens?
A. Yes.
Q. Are there -- are you aware of any epitopes that are shared or any antigenic determinants that are shared between HCV and any Flavivirus?
A. I don't -- I'm not aware of that.
Q. Are you aware of any epitopes that are shared between HCV and any other virus at all?
A. That is, again, you can ask "any," that is very difficult question for me to answer. So give me some kind of number.
So the tests, there is no such thing as absolute here. It's all statistic. So if you run million tests, how many do you see? So I cannot say, okay, it's absolutely zero. I cannot tell you

that.
So give me example and then I will tell you.
Q. So your answer is that you are not, as you sit here today, you are not aware of any antigenic determinants that are found both in HCV and in any other virus?
A. I didn't say that. I think all the tests will have some false positive, but we do pick up the hepatitis C. That is the most important here.
The test is specific for C, and then we don't say there is no false positive.
There's no test that is absolutely --
Q. What sort of thing causes false positives?
A. That depend on what kind of disease. Could be anything.
Q. Are there certain types of viruses that cause false positive results?
A. I don't know. We don't know.
If you want me to give you example, there is Kansas City. There's a nun donated blood for more than ten years, didn't cause any hepatitis in the recipient.
When we run the tests, we see hepatitis C, first generation, C-100. We pick up the sample.
So I say no, this is not hepatitis C because

the most important is the recipient didn't develop the disease. How come the nun get the antibody against -- actually, we narrow it down to 5-1-1 region. We don't know.
We are dealing with heterogeneous population. We are not dealing with homogeneous population here.
Q. And so you're not aware of what the nun was exposed to that caused antibodies that recognized 5-1-1?
A. No.
MR. RABINOWITZ: Okay. I think this is probably a good time for a break.
THE VIDEOGRAPHER: Going off record. Time now is 3:04.
(Recess.)
THE VIDEOGRAPHER: Going back on record. Time now is 3:23.
MR. RABINOWITZ: Q. Dr. Kuo, let me direct your attention once again to Exhibit 200, the '596 patent, and again to Column 8, towards the end, Line 12. It refers to the presence of co-linear peptide sequences that are conserved with HCV-1.
Would you explain what that means.

A. So it's linear peptide sequence conserved with hepatitis C-1.
Q. What are co-linear peptide sequences?
A. It's just the primary amino acid sequence.
Q. And what does the term "co-linear" convey?
A. That, I don't know. I didn't use that in the work, so I don't know.
Q. Would you agree that that refers to sequences or motifs that are found in different parts of different regions of a polypeptide?
MR. GRECO: Objection.
THE WITNESS: No, I don't know. I could not answer your question.
MR. RABINOWITZ: Okay, thank you.
Q. Now, going back to the various criteria that we have been discussing, an ORF of approximately 9,000 nucleotides to approximately 12,000 nucleotides, a polyprotein similar in size to that of HCV-1 encoded polyprotein of similar hydrophobic character, encoded --
(Reporter interruption.)
MR. RABINOWITZ: Q. -- polyprotein of similar antigenic character to HCV-1, presence of co-linear peptide sequences conserved with HCV-1, those

are five different criteria.
Must a candidate virus possess all of those to qualify as an HCV-1?
MR. GRECO: Object to the form.
THE WITNESS: Personally, I don't think so. I think that is the criteria you can use.
MR. RABINOWITZ: Q. Are these just examples of criteria?
A. What do you mean by "examples of criteria"?
Q. Well, I see that the patent says, "These would be defined as HCV according to various criteria such as, for example," and then it mentions all of those.
A. Yes, already described here, "for example."
Q. So these are just examples. There are other criteria one can use instead?
MR. GRECO: Object to the form.
THE WITNESS: Maybe.
MR. RABINOWITZ: Q. What would those other criteria be?
A. That, I don't know.
Q. As far as you're aware, are other criteria spelled out in this patent for classifying a virus as an HCV-1?

MR. GRECO: Objection to form.
THE WITNESS: And this paragraph already mentioned this is "defined as HCV according to various criteria, such as."
So we already describe here.
MR. RABINOWITZ: Q. They describe some, but there are others as well. Right? These are for example.
A. There could be.
Q. And I'm asking whether you can point to any other part of the patent that lists other criteria.
A. I didn't read the patent. I just read now, so I could not tell you. I could not answer.
Q. Okay. Let's go to the next paragraph in Column 8, where it says:
"All HCV isolates encode at least one epitope which is immunologically identifiable (i.e., immunologically cross-reactive) with an epitope encoded in the HCV cDNAs described herein."
Firstly, do you agree that this is a criterion that an isolate needs to satisfy to be classified as an HCV?
A. But already described in previous paragraph

in antigenic character.
Q. But I'm asking you, is it necessary for a virus to encode at least one epitope which is immunologically identifiable with an epitope encoded in the HCV cDNAs described in this patent in order to qualify it as an HCV?
A. It's just for patent say here.
Q. That's what the patent says. Right?
A. Yes.
Q. And so if a candidate virus does not encode at least one epitope which is immunologically cross-reactive with an epitope encoded in the HCV cDNAs in the patent, then it would not be an HCV. Right?
A. No, your question is too vague. I could not answer.
So you will try to tell me if you find some negative result, doesn't react with one of the HCV-1 protein, and then you will say, okay, this is not HCV, I don't accept that.
Q. Well, then what does it mean when it says all HCV isolates encode at least one epitope which is immunologically identifiable --
A. That is English. It say this one. You have to look a lot of the epitope.

So when you didn't see, for example, like 5-1-1 region, if the patient has no antibody against 5-1-1 region, I will not say that is not -- necessarily is not an HCV infection. You have to look at other region.

Q. But if you look hard enough, you will find at least one?

A. Yes.

Q. And that's a characteristic of HCV. Right?

A. No. Patient infected with hepatitis C, generate similar immune system to make antibody. When you don't see the antibody, doesn't mean he's not infected with HCV.

Q. I'm not talking about the patients now. I'm talking about a virus that's been isolated.

I'm trying to classify it to see whether it's an HCV within the meaning of the patent or not an HCV within the meaning of the patent. Now, the patent says:

"All HCV isolates encode at least one epitope which is immunologically identifiable...with an epitope encoded in the HCV cDNAs described herein."

My question to you is, if this new virus

I've isolated does not possess at least one epitope which is immunologically cross-reactive with an --

(Reporter interruption.)

MR. RABINOWITZ: Q. My question is, if this new virus is -- does not encode at least one epitope which is immunologically cross-reactive with an epitope encoded in the HCV cDNAs described in this patent, can I conclude it is not an HCV?

A. No, you cannot conclude that. Because when you express the cDNA in different organism, your antigen may be different.

So when you use the antigen to pick up antibody, you see there's no cross-reaction, doesn't mean it's not -- there's no epitope there, because maybe you denature it, maybe your expression system different.

What I try to say is negative result, you cannot conclude it's negative.

Q. I see.

How did you know, you and your co-inventors, that all HCV isolates encode at least one epitope which is immunologically identifiable with an epitope encoded in the HCV cDNAs described in your patent?

MR. GRECO: Object to the form.

THE WITNESS: We just described here encoded this one. So could be more than one.

MR. RABINOWITZ: Q. But how did you know that applied to all HCV isolates?

A. It's described in the patent.

I don't know your question.

Q. Well, it says that all HCV isolates encode at least one epitope which are immunologically identifiable with an epitope encoded in the HCV cDNAs described in the patent.

I'm asking how you and your co-inventors knew that that applies to all HCV isolates?

A. We defined this as hepatitis C. It doesn't encode it at one epitope. It's not in our patent.

Q. Okay. Now, it says:

"Preferably the epitope is contained in an amino acid sequence described herein and is unique to HCV when compared to previously known pathogens."

The fact that you used the word "preferably," does that mean that the epitope does not need to be unique to HCV when compared to previously known pathogens?

MR. GRECO: Object to the form.

THE WITNESS: I could not answer this.

MR. RABINOWITZ: Q. Could you tell me why the word "preferably" was used in that sentence?

A. No, I could not.

Q. Would you not be able to agree that it means that the epitope could be shared between HCV and other pathogens?

A. If you look hard enough, you will find, because the size of epitope is only five amino acid. So the chance to get five amino acid in similar is 25 power.

So if you look hard enough, yes, you can probably see it.

Q. And if you inject it into enough animals?

A. Yeah. I just mentioned the example about Kansas City nun's story, so.

Q. So you would conclude, based on your expertise in immunology, that HCV shares at least some epitopes with some other viruses?

A. I didn't say that. I think if you look hard enough, but the question we are dealing here is human disease is broad.

So are those virus -- your theoretical virus

coexist with C in our blood supply? If they exist, our tests is doing very well. So we didn't have too much problem.

Q. Now, I'm going to direct your attention to the next paragraph in Column 8, which says:

"HCV strains and isolates are evolutionarily related. Therefore, it is expected that the overall homology of the genomes at the nucleotide level may be about 40% or greater..."

And then the sentence continues:

"...probably will be about 50% or greater," and so on.

Just read that entire sentence to yourself.

MR. GRECO: Maybe read the whole paragraph.

MR. RABINOWITZ: And anything else you want to read to yourself, too, and let me know when you're finished doing that.

THE WITNESS: Yes.

MR. RABINOWITZ: Q. Is there a minimum overall homology of the genome at the nucleotide level that a candidate virus must satisfy in order to be classified as an HCV?

A. It's already described in this paragraph.

Q. Well, the paragraph says -- isn't it true the paragraph says it is expected that the overall homology may be about 40% or greater?

A. Yes.

Q. It doesn't say that it must be 40% or greater.

MR. GRECO: So what's the question now?

MR. RABINOWITZ: Q. It's true, it does not say that it must be 40% or greater. Right?

A. Yeah, that says may be.

Q. May be. Does that mean that a candidate virus must be at least 40% homologous at nucleotide level to qualify as HCV?

A. No, it says just may be, didn't say must be.

Q. So a candidate virus can qualify as an HCV even if it doesn't have at least 40% overall homology at nucleotide level. Right?

A. But we just set up the criteria in the first paragraph of Column 8.

Q. I'm asking about the criterion of overall homology at nucleotide level. We've not discussed that before.

My question to you is this. If it satisfies

various other criteria, it need not be at least 40% homologous at nucleotide level overall to HCV-1 to be classified as an HCV. Right?

A. In here it just says may be about 40% or greater.

Q. So that's not a necessary qualification to satisfy the definition of HCV. Right?

A. From nucleotide sequence, that is true.

Q. Right. So just to make sure I understand your answer correctly, it's not a requirement for classification as HCV that the candidate virus must necessarily have at least 40% overall homology at the nucleotide level. Is that right?

A. But are you going to abandon criteria in the first paragraph of Column 8?

Q. I'm talking about in addition to whatever other criteria apply. I'm just asking whether at least 40% homology of nucleotide level --

A. But my answer is you have to satisfy the first paragraph criteria, then this nucleotide sequence is separate.

Q. Good, and so my question --

A. It may be 40%.

Q. So my question to you is, if the first

paragraph of Column 8 is satisfied, then it is not necessary for a virus to have at least 40% homology at nucleotide level to qualify as an HCV. Right?

A. May be 40% or greater homology. That is what it say here.

Q. Could it be less than 40%?

A. That is your assumption. We just say it may be 40% or greater, but if you want to say 40% or less, that is your assumption here.

Q. Well, that's why I'm asking you whether that is correct. Is that a correct assumption?

A. But we didn't say that in here.

Q. What you said is that the overall homology may be about 40% or greater.

A. Yes.

Q. I'm asking you, is 40% homology a prerequisite in order to classify a virus as HCV?

MR. GRECO: Objection to the form.

THE WITNESS: I could not answer your question. We say, okay, should be greater than 40%. And then you want to make an assumption is under 40%, ask my opinion.

We didn't say anything about under 40%, so it's difficult for me to say anything.

You assume something here, and we didn't say any -- 40% -- if we say -- if 40% is not HCV, I will say, yes, we say that, but we didn't say. When we didn't say anything, we cannot say we say something.

MR. RABINOWITZ: Can I ask the reporter to read back the last two sentences of that answer.

(Record read.)

MR. RABINOWITZ: Q. So do you agree that the patent does not say that the overall homology at the nucleotide level must be 40% or greater?

MR. GRECO: Object to the form.

THE WITNESS: May be 40% or greater, that is said in the patent.

MR. RABINOWITZ: Q. The patent does not say it must be 40% or greater, right?

A. In a word, that's true, but I don't know in legal explanation.

Q. Let me go back to the preceding paragraph, which discusses epitopes of HCV isolates.

Does the patent say that all HCV isolates have at least one epitope in common with all other HCV isolates?

MR. GRECO: Objection to the form.

THE WITNESS: No. All HCV isolate encode

at this one epitope which is immunologically identifiable.

MR. RABINOWITZ: Q. Does that mean with --

A. With epitope encoded in HCV cDNA described herein.

Q. What my question is, is there at least one epitope that is common to all HCV isolates, is that what that sentence means?

A. No, I don't think that is what the sentence means.

Q. Does the sentence mean that HCV can share, call it epitope 1 with a particular HCV isolate, and may share epitope 2 with a different HCV isolate, and share epitope 3 with yet a third HCV isolate, but not necessarily the same one epitope with all of them?

MR. GRECO: Object to the form.

THE WITNESS: For example, if there's a hundred epitope of hepatitis C, type 1, if you want to say this unknown hepatitis C, the question is, do they have one of the epitope similar to the HCV-1?

If the answer is yes, this one similar to the type 1, we'll claim that it's hepatitis C.

MR. RABINOWITZ: Q. And the second isolate may share a different epitope with HCV-1?

A. May be same, may be different.

Q. So it's not required that they all share the same, at least one epitope in common with each other. Right?

A. That is my interpretation.

Q. Good, thank you. Let me direct your attention back to the claims of the '596 patent. Actually, we're going to move on to Column 55, Claim 22.

Would you read that claim over, and I'm going to focus on the phrase "a unique nucleotide residue sequence."

What does that mean, "a unique nucleotide residue sequence"?

MR. GRECO: Object to the form.

THE WITNESS: It's just unique sequence.

MR. RABINOWITZ: Q. What does that mean, "unique"?

A. There's only one sequence, all right?

Q. Do you mean the sequence is only found in HCV and not other viruses?

A. No, didn't say that.

Q. Well, then what does "unique" mean?

A. If you dissect 9kb HCV-1 sequence, so

certain region is 5 or 10 nucleotide, it's only found in hepatitis C. So that is --

Q. And not found in anything other than your hepatitis C?

A. But what I try to say is not particular region. You have to look all of them.

Q. So that's referring to a particular region of hepatitis C that's --

A. No, I didn't say particular region.

MR. RABINOWITZ: Dr. Kuo, I'm going to ask you let me finish my question before you answer. I know sometimes it's difficult, but I will ask you to do that.

Q. My question is, it says:

"...a contiguous sequence of at least 10 nucleotides fully complementary to a unique nucleotide residue sequence in either strand of the nucleotide residue sequence depicted in Figure 1."

Does that mean that there's a sequence of at least 10 nucleotides in -- depicted in Figure 1 that's found only in HCV?

MR. GRECO: Objection.

THE WITNESS: You have to work through

all the genome. Make all the 10, 10-mer, and then see, okay, this is unique to the hepatitis C.

MR. RABINOWITZ: Q. How do you tell whether it's unique to hepatitis C?

A. It's only found in hepatitis C.

Q. What do you have to compare it with?

A. Compare with all the isolates. So you give me a hypothetical region.

Example. Okay, if you have a sequence, okay, similar or unique -- similar to type 1, am I going to call that hepatitis C?

I say, well, you have to look all the sequence. We didn't give you the particular sequence here, so you have to compare all the 10 nucleotide.

Q. Let me ask you this. If I provide you with an oligonucleotide that is perfectly complementary to, let's choose a sequence of HCV, let's say nucleotides 100 through 110 as depicted in Figure 1, and I ask you, "Is such an oligonucleotide fully complementary to a unique nucleotide residue sequence in either strand of Figure 1," how would you determine whether that particular oligonucleotide satisfies that criterion of uniqueness?

MR. GRECO: Sorry. Objection.

THE WITNESS: So you just pick up randomly 10 polynucleotide, is homology to the HCV-1?

MR. RABINOWITZ: Q. It's perfectly complementary to HCV-1. But my question is, what tests do you need to do to see whether it fulfills this claim, satisfies this claim?

MR. GRECO: Objection.

THE WITNESS: And where you get the sequence? Is it synthesized randomly, or you pick up the sequence from isolate?

MR. RABINOWITZ: Q. Let's say that it's synthesized randomly. What tests do you need to do?

A. 10 oligonucleotides? We didn't claim that. That is not virus.

Q. I beg your pardon?

A. That oligonucleotide is not virus. You just synthesized it.

Q. Well, let's take a look at Claim 22. It talks about the purified preparation of Claim 1.

If I look back at Claim 1, Claim 1 is directed to a purified preparation of an oligonucleotide that satisfies certain limitations.

And then it says, wherein the oligonucleotide comprises a contiguous sequence of at

least 10 nucleotides fully complementary to a unique nucleotide residue sequence in either strand of the nucleotide residue sequence depicted in Figure 1.

Do you agree that Claim 22 is directed to a preparation of an oligonucleotide?

MR. GRECO: Objection to the form.

THE WITNESS: Yes.

MR. RABINOWITZ: Q. It can be a synthetic oligonucleotide --

A. But you need Figure 1 to synthesize it. You cannot randomly synthesize it.

Q. Okay, now here is my example. Based on Figure 1, I've synthesized an oligonucleotide that is perfectly complementary to nucleotides 100 through 110 in Figure 1.

How do I determine whether such a preparation of an oligonucleotide satisfies the requirements of Claim 22 as far as uniqueness is concerned?

MR. GRECO: Objection.

THE WITNESS: But you've already used the sequence in Figure 1 to synthesize the oligonucleotide. So I don't understand your question here.

MR. RABINOWITZ: Q. Will such an

oligonucleotide preparation be complementary to a unique nucleotide sequence?

A. In a particular case, yes. But you have to start it. You cannot just pick up randomly.

Q. So I'm trying to find out, is anything that's perfectly complementary to at least 10 nucleotides of Figure 1 going to be unique within the meaning of this claim?

MR. GRECO: Objection.

THE WITNESS: If you synthesize 10 nucleotide randomly without look at the sequence in Figure 1, I will say no.

MR. RABINOWITZ: Q. No, Dr. Kuo, that is not my question.

I'm saying if I choose an oligo that's identical to any randomly chosen 10-mer in Figure 1, will that necessarily satisfy the requirement of uniqueness in Claim 22?

MR. GRECO: Objection.

THE WITNESS: I still cannot understand your question.

MR. RABINOWITZ: Let me come at it another way.

Q. What is the meaning of "unique" in Claim 22

as you understand it?

MR. GRECO: Objection.

THE WITNESS: As I understand, that is use the Figure 1 sequence to make that 10 nucleotide.

MR. RABINOWITZ: Q. That's what "unique" means?

A. As I understand, yes.

Q. Okay. Let me direct you to Column 9, Line 6. The two sentences beginning on Line 6. Of course, read anything else around it that you need to for context.

Please let me know when you've finished looking.

A. Yes.

Q. So it says:

"...the sequence of the region from which the polynucleotide is derived is homologous to or complementary to a sequence which is unique to an HCV genome. More preferably, the derived sequence is homologous or complementary to a sequence that is unique to all or to a majority of HCV isolates."

And then it goes on to describe various

techniques for determining whether a sequence is unique to the HCV genome.

Does that help clarify what the term "unique" means --

MR. GRECO: Objection.

MR. RABINOWITZ: Q. -- in Claim 22?

A. It gives example. Several way to do it.

Q. So it says the sequence can be compared to known sequences of other viral agents.

A. Right.

Q. Why would one make that comparison in testing for uniqueness?

A. So what is your question? I confused here.

Q. My question is, doesn't this describe that a unique sequence must be one that's not found in other organisms besides hepatitis C virus?

MR. GRECO: Objection to the form.

THE WITNESS: Yes, I see that is one definition.

MR. RABINOWITZ: Q. Take a look at, I think it's Line 13 in Column 9. It says:

"For example, the sequence can be compared to sequences in databanks, e.g., Genebank, to determine whether it

is present in the uninfected host or other organisms."

Do you see that?

A. Yes.

Q. Don't you agree, if the sequence is present in the uninfected host, it wouldn't be unique to HCV, would it?

A. And that, we will not use that as a primer.

Q. So a unique sequence must be present in HCV, but not in the uninfected host. Right?

MR. GRECO: Objection to the form.

THE WITNESS: That is when you want to use that to develop the test. So it's a different question here.

I keep saying, if you look hard enough, maybe you will see the homology between HCV virus and maybe virus from alligator or something, but we are dealing with a human disease here.

So if we want to diagnose human disease, we want to use HCV sequence that is unique to HCV, is not found in the host cell or not found in other virus. So that is our definition.

MR. RABINOWITZ: Q. Okay. So unique means it's not found in the host cells or in other viruses.

Right?

MR. GRECO: Object to the form.

THE WITNESS: To develop the test. It's just for practical meaning.

MR. RABINOWITZ: Q. So I'm not sure whether you are agreeing with me that a unique sequence means a sequence that's found in HCV but not in the host or in other viruses.

A. The oligonucleotide is used for other purpose.

For that purpose, we have to use this unique sequence for the HCV, not for other virus. So that is for the practical purpose. We are not talking about theoretical here.

Q. I just want to go back for a moment to Column 8, the paragraph beginning Line 16 concerning epitopes.

Does the patent provide or describe any reference serum that can be used to determine whether a candidate virus shares an epitope with HCV -- HCV-1?

MR. GRECO: Objection.

THE WITNESS: So can you read back the question?

(Record read.)

THE WITNESS: I don't understand your question at all, sorry. Maybe you have to rephrase it.
MR. RABINOWITZ: Okay, let me try it again.
Q. Are there standard sera that you can use in order to classify a candidate virus as HCV or not HCV?
A. No, there is no standard serum.
Q. No standard serum. Does the patent provide a particular serum as a reference serum to use in determining whether a newly isolated virus shares a common epitope with the cDNAs described in the patent?
A. I still don't understand your question. What do you want to get to?
For example, like if you want to get the HCV isolate, the first thing is use our immunoassay to pick up is there an antibody. Then if there's antibody, then try to sequence it, try to clone it.
So you try to say, okay, if there's a -- we don't have a panel set up by reference lab or something. If you pass this panel, then you say hepatitis C. If you don't, it's not.
No, we don't have that.
Q. And you don't have a panel defined in the patent itself?
A. No, but in here it is described different.

That's why I'm confused with your question here.
Encoded at least one epitope which is immunologically identifiable. So that is the sentence, with the epitope encoded in HCV cDNA library described here.
Q. Now, in order to test whether it encodes at least one epitope which is immunologically identifiable, you need to use at least one antiserum to test that. Right?
A. Right.
Q. Or a monoclonal antibody. Right?
A. Right.
Q. Does the patent tell you which monoclonal antibodies you can use or which sera you can use to do that testing?
MR. GRECO: Objection to the form.
THE WITNESS: This one percent of the total population in the world infected with hepatitis C. There's plenty of serum you can use, so I don't know what is -- why we have to provide an antiserum to identify it.
MR. RABINOWITZ: Q. Is that why the patent doesn't specify a particular serum or antibody to use?
A. It just tell you, say, okay, describe what

is our territory. So we say encode at least one epitope which is immunologically identifiable. And that is -- it's not particular technology. You can use different way to do it.
Q. Okay. And so in order to look at the epitope encoded in the HCV cDNAs described in the patent, you'd have to express the cDNAs and then make antibodies against them, wouldn't you?
A. Not necessarily.
MR. GRECO: Object to the form.
Go ahead.
MR. RABINOWITZ: Q. What would you have to do?
A. You can screen the human serum sample to find out is this serum react with this protein or not. Once it react, this is this antibody.
Q. If you pick up -- are you saying that immune serum is specific for HCV encoded epitopes?
A. No, I didn't say that.
Q. Isn't it true that serum from patients with HCV would contain antibodies to things that are not encoded in the cDNAs described in the patent?
A. No, I didn't say that. What I say --
You give me the example, say if you clone

the cDNA, express the protein. All right?
I say once you have that protein, you can identify the patient serum which will contain antibody against that protein. If necessary, you can phage or purify that antibody, and become a mono-specific serum.
Q. I'm interested in the first step of what you said. You said you clone the cDNA and then you express it.
A. Right.
Q. Does it matter what cells you express the protein in?
A. Of course it matter, yes.
Q. What difference does it make what cells you express the protein in?
A. Well, you express in -- it depend on which gene you want to express. You want to express E1, E2, it's a glycosylate. You better express in mammalian cell.
Q. What happens if you express it in yeast?
A. In yeast, it's non-glycosylate.
Q. In yeast it's not glycosylate?
A. Internal is not glycosylate.
Q. If you express it in bacteria, will it be glycosylate?

A. No, of course not.
Q. Will all mammalian cells glycosylate it the same?
A. We use particular ones, CHO cells. C-H-O cells will glycosylate same as human.
Q. What other cells could you use instead of CHO cells?
A. Why you want to use other cell?
Q. I'm just asking what other cells you could use.
A. No, you can use other different cell, like baculovirus system.
Q. What about BHK cells, could you use those?
A. If you want. That is a personal choice. There's no reason you use, but CHO cell has been used in common.
Q. Will BHK cells glycosylate cDNAs in the same way as CHO cells?
A. That, I cannot tell you. I don't know.
Q. Would it make a difference to the epitope if the glycosylation was different?
A. Maybe.
Q. Would it make a difference to the epitope if the glycosylation was absent?

A. For some epitope, yes.
MR. RABINOWITZ: I think it's been about an hour since we began. Let's take a short break and then maybe we can --
MR. GRECO: Go for the home stretch.
MR. RABINOWITZ: -- go for the home stretch.
THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, this marks the end of Videotape 3. Going off record, the time now is 4:11.
(Recess.)
THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, Ph.D., this marks the beginning of Videotape 4. Going back on record, the time now is 4:21.
MR. RABINOWITZ: Q. Dr. Kuo, let me direct your attention for a moment to Exhibit 202. That's the amendment dated February 27, 1995.
And also to Exhibit 203, which is the '714 application, at Page 15 of that application.
MR. GRECO: You say 202 and 203. This is 203. This is --
THE WITNESS: 202.
MR. GRECO: 202 is 202. These two is what you need.

MR. RABINOWITZ: Q. So Exhibit 202, Page 11. The first bullet point. Do you see there, it says:
"...a 'purified preparation' is defined in the '714 application at page 15, lines 8 to 17."
Do you see that?
A. Yes.
Q. Would you turn to Page 15, Lines 8 to 17 of the '714 application, Exhibit 203.
A. Yes.
Q. Do you agree that a purified preparation of viral polynucleotide refers to a non A, non B virus genome or fragment thereof which is essentially free of polypeptides with which the viral polynucleotide is naturally associated?
MR. GRECO: Object to the form.
THE WITNESS: So what is your question?
MR. RABINOWITZ: Q. Do you agree with that definition?
A. Yes.
Q. Do you agree that "polynucleotide" in the '596 patent means the same thing as "oligonucleotide"?
MR. GRECO: Object to the form.

THE WITNESS: That's why I answer earlier on, I think different people got a different definition. So polynucleotide, oligonucleotide tend to overlap in term of size.
MR. RABINOWITZ: Q. You agreed earlier that "polynucleotide" as defined in the '596 patent meant "a nucleotide sequence regardless of its length." Is that correct?
A. No, I don't think I mentioned that.
Q. Let's see if I can take you back to Exhibit 200, which is the '596 patent. Column 9, Line 47.
A. Yes.
Q. So you agree "polynucleotide" means "nucleotides of any length"?
A. It's defined in here, polymeric form.
Q. So do you agree that there's no minimum length for a polynucleotide as defined here?
A. From the patent, it looks like that.
Q. So as used in the patent, "polynucleotide" has the same meaning as "oligonucleotide." Right?
MR. GRECO: Object to the form.
THE WITNESS: I could not make that answer because I didn't read whole patent, so I cannot

answer.

MR. RABINOWITZ: Q. Now, with respect to Claim 1 of Exhibit 200, which is the '596 patent, do you agree that the meaning of "purified preparation" is given in Exhibit 203, which is the '714 application, Page 15, Lines 8 to 11?

MR. GRECO: Objection.

THE WITNESS: No. This is -- says, purified preparation of viral polynucleotide.

And in the Claim 1 is purified preparation of an oligonucleotide.

MR. RABINOWITZ: Q. Now, take a look at Exhibit 202, Page 11, the first bullet point.

A. Yes.

Q. Do you see it says, "A purified preparation of an oligonucleotide"?

A. Yes.

Q. Is that the same as the text of -- the initial text of Claim 1 on Column 52 of the '596 patent, "A purified preparation of an oligonucleotide"?

A. Yes.

Q. Okay, let's go back to Exhibit 202. It continues. "...a 'purified preparation' is defined in the '714 application at page 15, lines 8-17." Right?

A. All right.

Q. So let's go to --

So do you agree that the definition of "purified preparation" on Page 15, beginning at Line 8, applies to the term "purified preparation" in Claim 1 of the '596 patent?

MR. GRECO: Objection.

THE WITNESS: Could you read back the question, please.

(Record read.)

THE WITNESS: Yes, that is one way to define purified prep of the oligonucleotide.

MR. RABINOWITZ: Q. And so "purified preparation" in Claim 1 means "a preparation which is essentially free of polypeptides with which the viral polynucleotide is naturally associated." Correct?

MR. GRECO: Objection.

THE WITNESS: But they say before that, they refer to non A, non B genome or fragment.

MR. RABINOWITZ: Q. So that part of the definition as well?

A. Yeah.

Q. So a purified preparation in Claim 1 is a purified preparation of a non A, non B virus genome or

fragment thereof, which is essentially free of polypeptides with which the viral polynucleotide is naturally associated?

MR. GRECO: Objection.

MR. RABINOWITZ: Q. Right?

A. Right.

Q. Let's go to Exhibit 200, the '596 patent, Claim 7.

We're finished with Exhibits 202 and 203 for the moment.

Could you read through Claim 7 and then explain to me what the meaning is of "a conserved HCV nucleotide sequence."

A. So what is your question here?

Q. Will you explain to me, please, what the term "conserved HCV nucleotide sequence" means?

A. That means the sequence is present in most of the isolate.

Q. The particular sequence is present in --

A. Yeah.

Q. When you say "most isolates," what do you mean by "most isolates"?

A. That is just most of the isolate. I didn't say 100% of isolate.

Q. What percentage would be required for a sequence to be conserved?

A. I could not tell you the percentage. I say this is a relative term.

When you say you are conservative, you are liberal, can you measure it? No way you can measure it.

It's the same thing. How can you measure? It's just relative.

Q. So how would someone be able to determine whether a particular sequence, a particular oligonucleotide, fell within the scope of Claim 7?

Let's say it was within the scope of Claim 1, but they wanted to test to see whether it was also within the scope of Claim 7. What test would they have to do to see whether it qualified as a conserved HCV nucleotide sequence?

A. You have to compare the sequence.

Q. With what?

A. With your isolate. So we have HCV, type 1 sequence here. If you have a new isolate, you compare two sequence, say which part is conserve. So that is a conserved region.

Q. So a conserved region is a region which is

exactly present both in HCV-1 and in the new isolate?
MR. GRECO: Object to the form.
THE WITNESS: Not exactly. So I say this is a relative term.
So you can say certain region, like nucleocapsid region, with a rate of conserve. So more likely we are very similar, only few amino acid will change.
MR. RABINOWITZ: Q. Where do you draw the line between conserved and not conserved?
A. We have no line to draw. It's just operational. It's practical.
You want to develop something, immunoassay. Why would you choose hepatitis core as the antigen? Because it's a relative conserve. So that is --
We cannot say, Okay, you have to meet this criteria in order to claim it is conserved. No, there is no line we can draw.
Q. Would you agree that a conserved HCV nucleotide sequence means a portion of the genomic HCV --
(Reporter interruption.)
MR. RABINOWITZ: Q. Would you agree that a conserved HCV nucleotide sequence means a portion of

the genomic sequence of HCV that has less genotype to genotype variability than the genome as a whole?
A. Yes, I agree with that.
Q. How do you determine how much --
So you need to compare it with the average variability of the genome. Right?
MR. GRECO: Object to the form.
THE WITNESS: Computer sequence.
MR. RABINOWITZ: Q. No, in order to --
So you compare the variability of the particular sequence with the variability of the genome as a whole. Is that what you're saying?
A. That depend on what you want to do.
You're asking me how you define the conserve region, and I just say, okay, compare two sequence. If there's a sequence very similar or is very -- the homology is very high, and then you say that is conserved region.
That is what I just explained to you.
Q. So very high homology?
A. I would say yes.
Q. Are you talking in the 80 to 90% homology?
A. No, I don't say. That depend on how you want to do with it. So I don't draw the line.

Q. You say for some purposes it might need to be 80 to 90%?
MR. GRECO: Object on form.
THE WITNESS: I don't know. As I mentioned very, very early, I'm not expert in nucleic acid diagnostic or doing this, so I can only give you my opinion.
MR. RABINOWITZ: Q. So in your opinion, would 30 to 40% be enough?
A. I'm not --
MR. GRECO: Objection.
THE WITNESS: I'm not doing it. If my hand is not dirty, I don't make any comment.
MR. RABINOWITZ: Q. So you can't say where one would draw the line?
A. I, personally, I don't know how to draw it. Someone else may be.
Q. Would you take a look at Exhibit 200, which is the '596 patent, at Column 18, Line 51, to Column 19, Line 5, and read through that to yourself. Column 18, Line 51.
A. Yes.
Q. To Column 19, Line 5.
MR. GRECO: Again, that starts in the

middle of a paragraph, so why don't you just --
(Simultaneous dialog.)
MR. RABINOWITZ: Read anything in the immediate area or elsewhere in the patent that you need to.
THE WITNESS: Yes.
MR. RABINOWITZ: Q. Does that passage tell you where to draw the line to determine whether a sequence is conserved or not?
MR. GRECO: Objection to the form.
THE WITNESS: That is describing the paragraph, so I have no way to judge. It is written by our patent attorney.
MR. RABINOWITZ: Q. When you as a scientist read that, do you know how to draw the distinction between a conserved sequence and a non-conserved sequence?
A. I just mentioned, I am not the expert in nucleic acid biochemistry here, so I could not answer.
Q. Okay. Let me draw your attention to the same patent, Line 33 (sic), Lines 23 to 32.
And, again, read anything that you need for context as well.
MR. GRECO: Is it Column 33?

MR. RABINOWITZ: Column 33, Lines 23 to 32.
THE WITNESS: Okay.
MR. RABINOWITZ: Q. Does that help you determine how much variability is permitted --
A. No. I still tell you same thing. This is done by somebody else, so I am in no position to judge.
Q. Who did that determination?
A. I really don't know. You better ask our patent attorney. There's so many people on the patents here, so.
Q. Does it not suggest to you that there should almost be no variation at all? It talks about identical except for one nucleotide.
MR. GRECO: Objection to the form.
THE WITNESS: I don't know. As I mention, I don't know anything, so how can I answer the question?
MR. RABINOWITZ: Okay.
Q. Let me take you now to the same patent, Column 49, Lines 51 to 56.
A. Which column?
Q. Column 49.
A. 49.
Q. Lines 51 to 56.

A. Okay.
Q. Does that tell you where to draw the distinction between a conserved and a non-conserved sequence?
A. No, again, same answer. This is not my territory.
Q. Let me draw your attention to Column 28, Line 64 to Column 29, Line 1.
MR. GRECO: Column 28? Again, please?
MR. RABINOWITZ: Line 64 to Column 29, Line 1, and we'd better mark the '671 patent as well.
MR. GRECO: Column 28. Over here.
MR. RABINOWITZ: Column 29.
MR. GRECO: 28, right? You started on 28.
MR. RABINOWITZ: Sorry, Column 28, Line 64, to Column 29, Line 1.
I'd like to ask the reporter to mark this as Exhibit 204, I believe.
(WHEREUPON, DEPOSITION EXHIBIT 204 WAS MARKED FOR IDENTIFICATION.)
MR. RABINOWITZ: Q. Does that passage from the '596 patent tell you anything about where to draw the line?

MR. GRECO: Objection to the form.
THE WITNESS: No, I could not answer, because this is another nucleic acid question.
MR. RABINOWITZ: Q. I'm going to ask you to look at Column 26 of the '596 patent, Lines 9 to 21. That's the paragraph beginning, "It is anticipated."
A. Okay.
Q. Does that tell you where to draw the distinction between a conserved and a non-conserved sequence?
MR. GRECO: Objection to the form.
THE WITNESS: This is very long paragraph, so you have to separate your question into separate, otherwise it's confusing.
MR. RABINOWITZ: Q. What's confusing about it?
A. Because in the last sentence or the paragraph we are mentioning about the Flaviviruses.
Q. And why is that confusing?
A. Because I don't want you to generalize from the -- my question to this, the last sentence. So you better ask the question separate.
Q. I don't understand. My question is whether this paragraph makes it clearer for you where -- how to

distinguish between a conserved and a non-conserved HCV sequence.
A. So that is, the paragraph say, just compare the nucleotide sequence -- or amino acid sequence with different isolate.
Q. Is that not enough information to allow you to distinguish between conserved and non-conserved sequences?
A. Again, I think that depend on where you want to draw the line.
Q. Okay. Right, I think we have finished for the moment with Exhibit 200.
Dr. Kuo, do you consider HCV to be a medically important disease?
A. Yes, I do.
Q. Extremely important?
A. Yes.
Q. Is it important to have a sensitive and accurate test for diagnosis of HCV infections?
A. That depend on what is your criteria. You satisfied with --
Before we have a test, you have 10% risk to get infected. Now the risk is 1 out of 125,000. Are you satisfied with that?

Q. What is your answer to that question?
A. Well, for a lot of people, I say that is tremendous. It's more than million people prevented.
So what is your question? You want to have zero tolerance? Yes, we'd like to have that. But in medical practice, there's no such thing as zero.
Q. In your opinion, are the nucleic acids based test for hepatitis C virus infection the best available tests for picking up and diagnosing HCV infection?
A. I don't think the nucleic acid test would request an immunoassay. Nobody there can abandon immunoassay.
Q. Are the nucleic acid based tests however also an important addition to the public health?
A. I will say so, yes. But it's the second safety net.
Q. I'm sorry?
A. Safety net, second. You have to screen immunoassay.
Q. Are the nucleic acid based tests important for assuring the safety of the blood supply?
A. Some way, yes.
Q. Are the nucleic acid based tests important for diagnosing and managing cases of HCV infection?

A. Could you repeat the question?
MR. RABINOWITZ: Could you read back the question, please.
(Record read.)
THE WITNESS: That, you are talking about a chronic patient here? You are talking about a treatment?
MR. RABINOWITZ: Q. I'm including everything to do with clinical cases of HCV infection.
A. Some case, yes. Some case, no.
Q. Wouldn't you agree that PCR-based nucleic acid tests are the best available technology for nucleic acid based detection of HCV infection?
MR. GRECO: Objection to the form.
THE WITNESS: Do you have some other tests as good?
MR. RABINOWITZ: Q. What tests do you consider as good --
A. TMA.
Q. -- as PCR? Are there any other tests that are as good?
A. The GenProbe test.
Q. Which test is that?
A. GenProbe.

Q. What technology does GenProbe's test use?
A. TMA.
Q. Apart from TMA, are there other technologies that are, in your opinion, as good as PCR?
A. As I say, I have no experience with the PCR, so I don't know. If you are to ask me, say, okay, use PCR to abandon immunoassay, I say no.
Q. I'm restricting my question now to the best nucleic acid based tests for hepatitis C virus.
A. I think the answer is maybe we can find one at the Moscone Center, there is an AABB meeting here. Because of the deposition, I missed the meeting.
They will present a lot of nucleic acid tests in the meeting, so.
Q. Based on your knowledge as you sit here today, not having attended the meeting, do you consider bDNA technology to be as good as PCR technology for testing HCV?
MR. GRECO: Objection. No foundation.
THE WITNESS: No, I am not here to compare the tests. I never run both tests, so it's difficult for me to judge.
MR. RABINOWITZ: Q. You do attend lots of meetings.

A. Yes, I do.
Q. You hear the results of research by other scientists, don't you?
A. Yes.
Q. And as far as you know, do you not agree that PCR is considered to be superior technology for diagnosis of HCV using nucleic acids than bDNA?
MR. GRECO: Objection. No foundation, asked and answered.
THE WITNESS: In what setting?
I've seen bDNA got a certain advantage versus PCR. So it depends on what do you want to do with it.
Are you going to use in the blood screening setting, or are you going to use in diagnostic setting? So they are different purpose.
MR. RABINOWITZ: Q. What advantages are you aware of that bDNA technology has over PCR technology --
A. More quantitative aspect.
Q. -- for diagnosing HCV infection?
A. I'm not here to defend the bDNA, so I don't know. I just want to tell you, as far as I know for the bDNA, you can quantitate the viral low in the

hepatitis C, so that is advantage.

PCR you have semi-quantitative, but not necessarily will match to the bDNA. So that is how much I know.

Q. Are you able to say whether or not you agree that PCR-based tests are the most sensitive for detecting HCV?

MR. GRECO: Same objection.

THE WITNESS: That, I don't know. Unless I just run it, I cannot judge.

You have to compare with other, so just only one say PCR is most sensitive, I have no way to judge.

That's why I say, if we go to the meeting now in Moscone Center, maybe we can find out.

MR. RABINOWITZ: Q. Dr. Kuo, does the '596 patent, Exhibit 200, set forth the entire genomic sequence of HCV-1?

A. It just give you the sequence in Figure 1, so I don't know.

Q. Do you know whether or not the sequence in Figure 1 is the entire, complete sequence of HCV-1?

A. I don't think that is important in this patent discussion here.

Q. I'm afraid you will have to answer the

unimportant questions as well as the important ones.

MR. GRECO: He's been doing that all day, I thought.

MR. RABINOWITZ: Q. Do you know whether Figure 1 sets forth the entire genomic sequence of HCV-1?

A. Figure 1 is --

MR. GRECO: Figure 1 of the patent. You're looking at part of Figure 1.

THE WITNESS: Right, 1L.

MR. GRECO: They have numbers after them. I don't know what those numbers are.

THE WITNESS: That is Figure 1 until 9,000-something.

MR. RABINOWITZ: Q. Do you agree that Figure 1 begins at minus 341?

A. Yes.

Q. And continues to 9,001, and then continues for a further line?

A. That's correct.

Q. Is that the complete genomic sequence of HCV-1?

A. That, I don't know.

Q. Does the '596 patent provide the entire

sequence of any HCV other than HCV-1?

A. Well, I didn't read the patent completely, so I don't know. I think more likely, it's not.

Q. So as far as you're aware, it does not?

A. Yes.

MR. RABINOWITZ: I don't know how long you want to continue. I've finished at least for the moment with the '596 patent. I can go on to another patent, or we can --

MR. GRECO: Well, if you're going to start a whole new area, it's 5:00, maybe it would be a convenient break time.

MR. RABINOWITZ: Okay.

THE VIDEOGRAPHER: In the deposition of Dr. George Kuo, this marks the end of Videotape 4. Going off record, the time now is 4:59.

(Ending Time: 4:59 p.m.)

CERTIFICATION

I, FRANCES A. WEINROB, duly authorized to administer oaths pursuant to Section 2093(b) of the California Code of Civil Procedure, do hereby certify: That the witness in the foregoing deposition was by me duly sworn to testify the truth in the within-entitled cause; that said deposition was taken at the time and place therein cited; that the testimony of the said witness was reported by me and was thereafter transcribed under my direction into typewriting; that the foregoing is a complete and accurate record of said testimony; and that the witness was given an opportunity to read and correct said deposition and to subscribe the same.

Should the signature of the witness not be affixed to the deposition, the witness shall not have availed himself/herself of the opportunity to sign or the signature has been waived.

I further certify that I am not of counsel nor attorney for any of the parties in the foregoing deposition and caption named nor in any way interested in the outcome of the cause named in said caption.

DATED: NOVEMBER 17, 1999

FRANCES ANN WEINROB, CSR 4029

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